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(56) Documents Cited
EP 0829225 A2      EP 0829224 A2      EP 0282234 A1
Medical & Biological Engineering & Computing, Vol.
31(3), pp. 284-290, May 1993 Physics in medicine and
biology, Vol. 38(12), pp. 1911-1922, Dec 1993

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UK CL (Edition P ) G1G GPB
INT CL$^6$ A61B 5/00 5/14 , G01N 21/17 33/483 33/487
33/49
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(54) Abstract Title
In-vivo photoacoustic measurement

(57) A biological parameter is measured by directing
laser pulses from a light guide (10) into a body part
consisting of soft tissue, such as the tip of a finger (12), to
produce a photo-acoustic interaction. Sound waves (14)
generated by absorption of the optical beam are detected
by a transducer (16). The detector and optical beam guide
are housed in a body-part shaped sensor head device
(figures 2 to 16), and are preferably not co-linear with one
another. Analysis of the transducer output enables
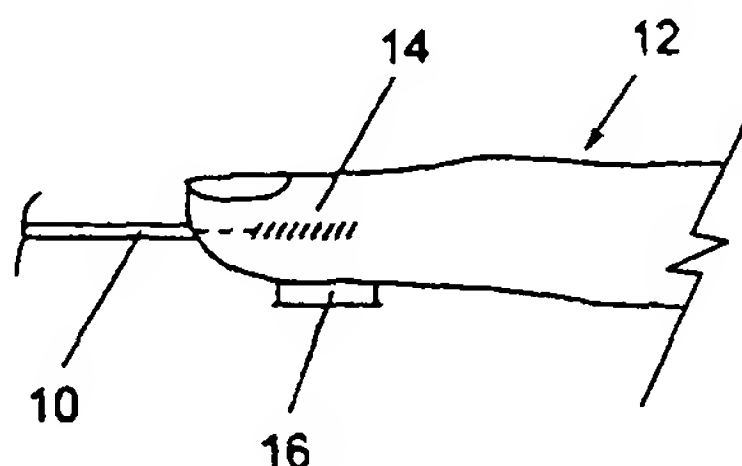calculation of the desired parameter, e.g. blood glucose
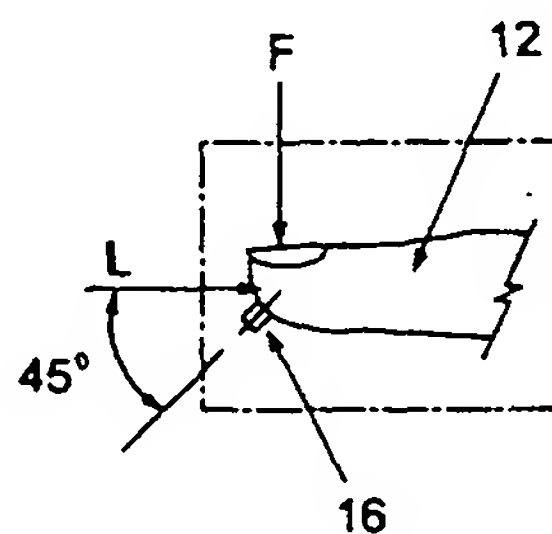concentration.
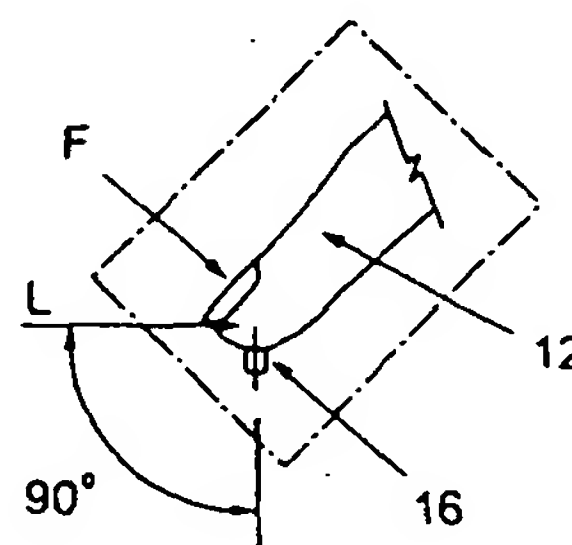
Fig. 1a



Fig. 1b



Fig. 1c

GB 2 322 941 A
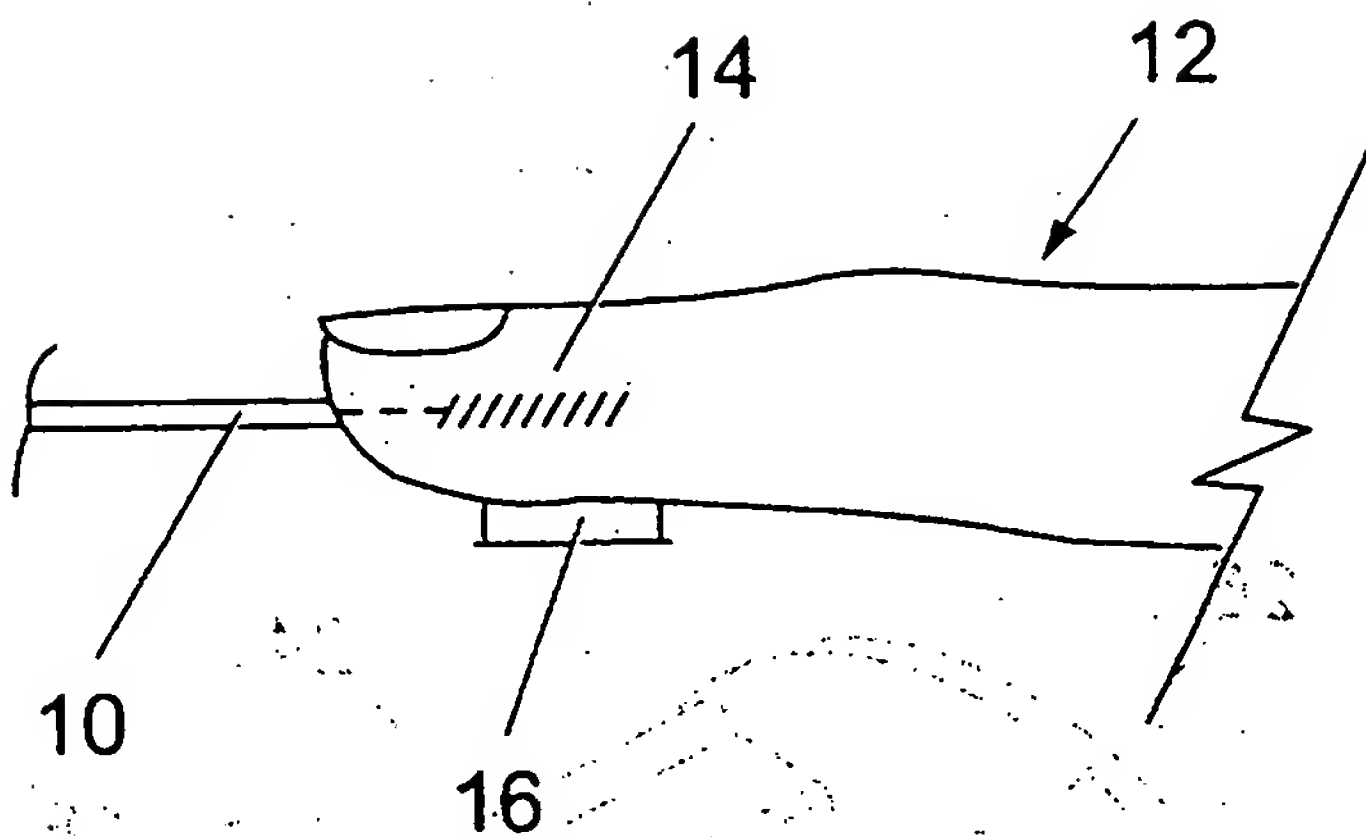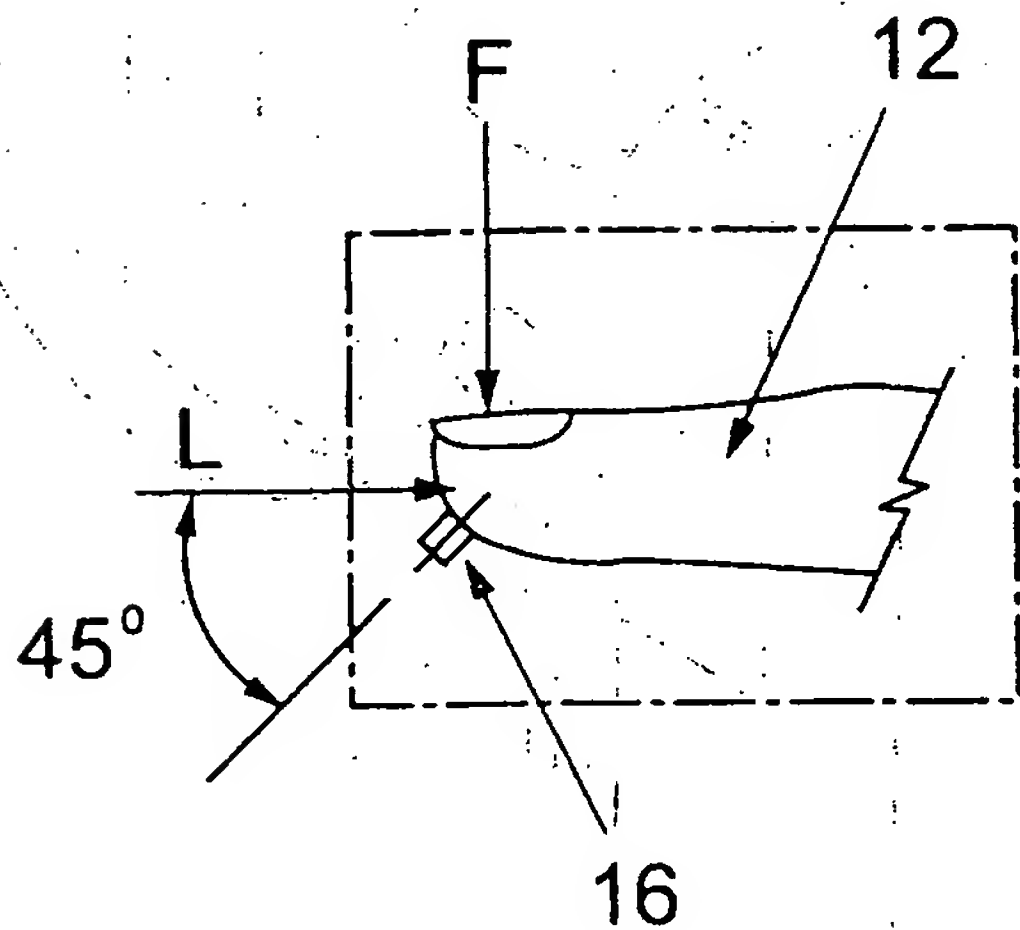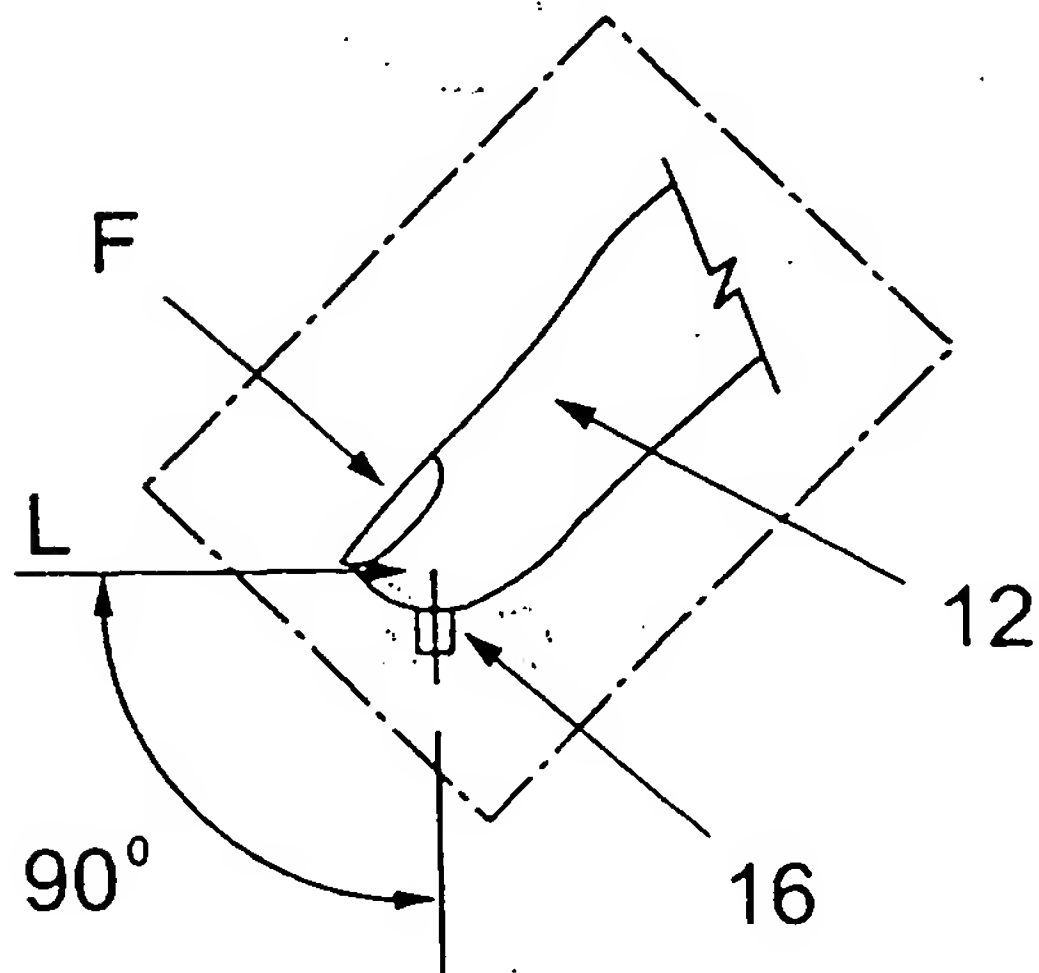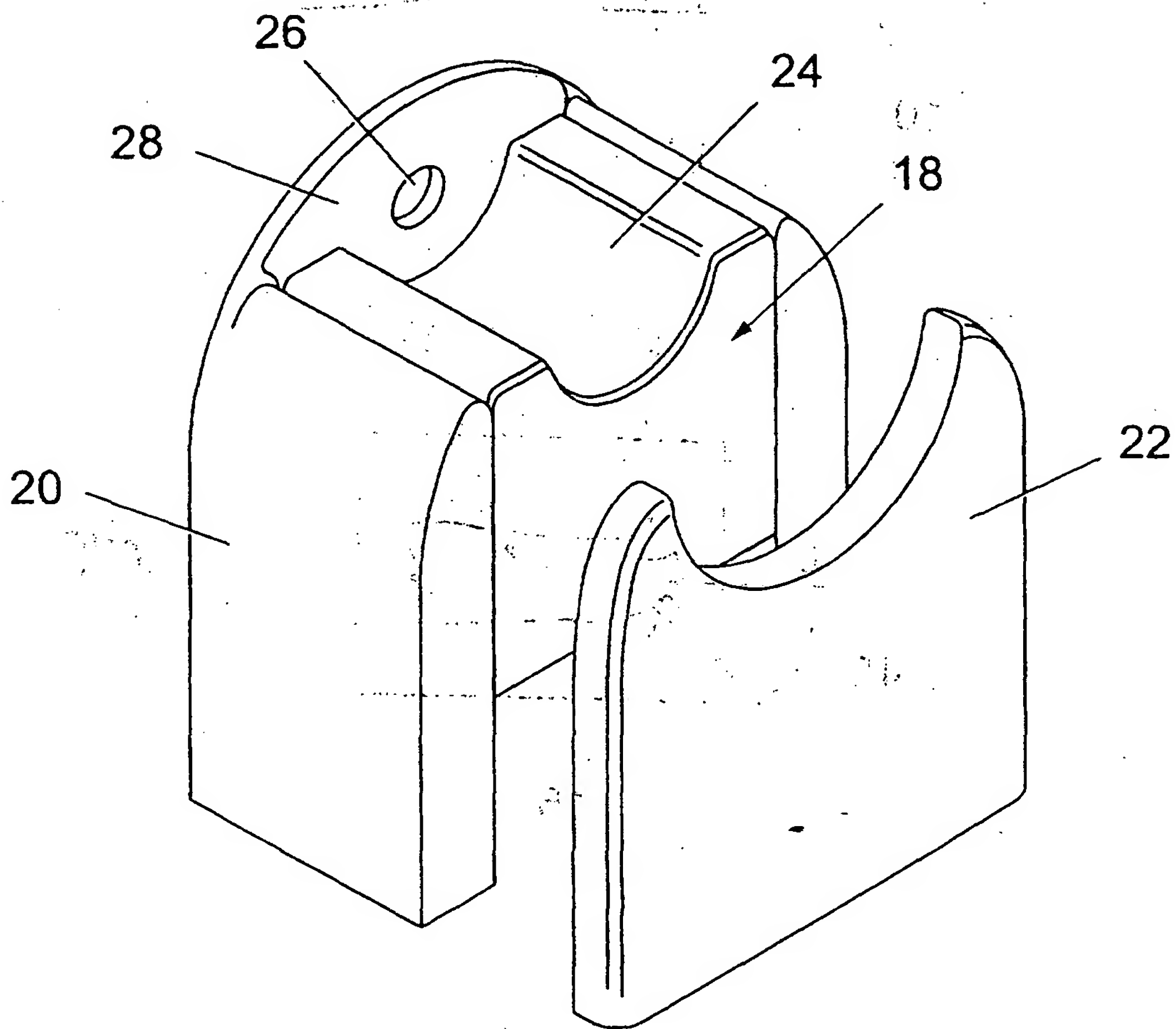
Fig. 1a



Fig. 1b



Fig. 1c

*Fig. 2*
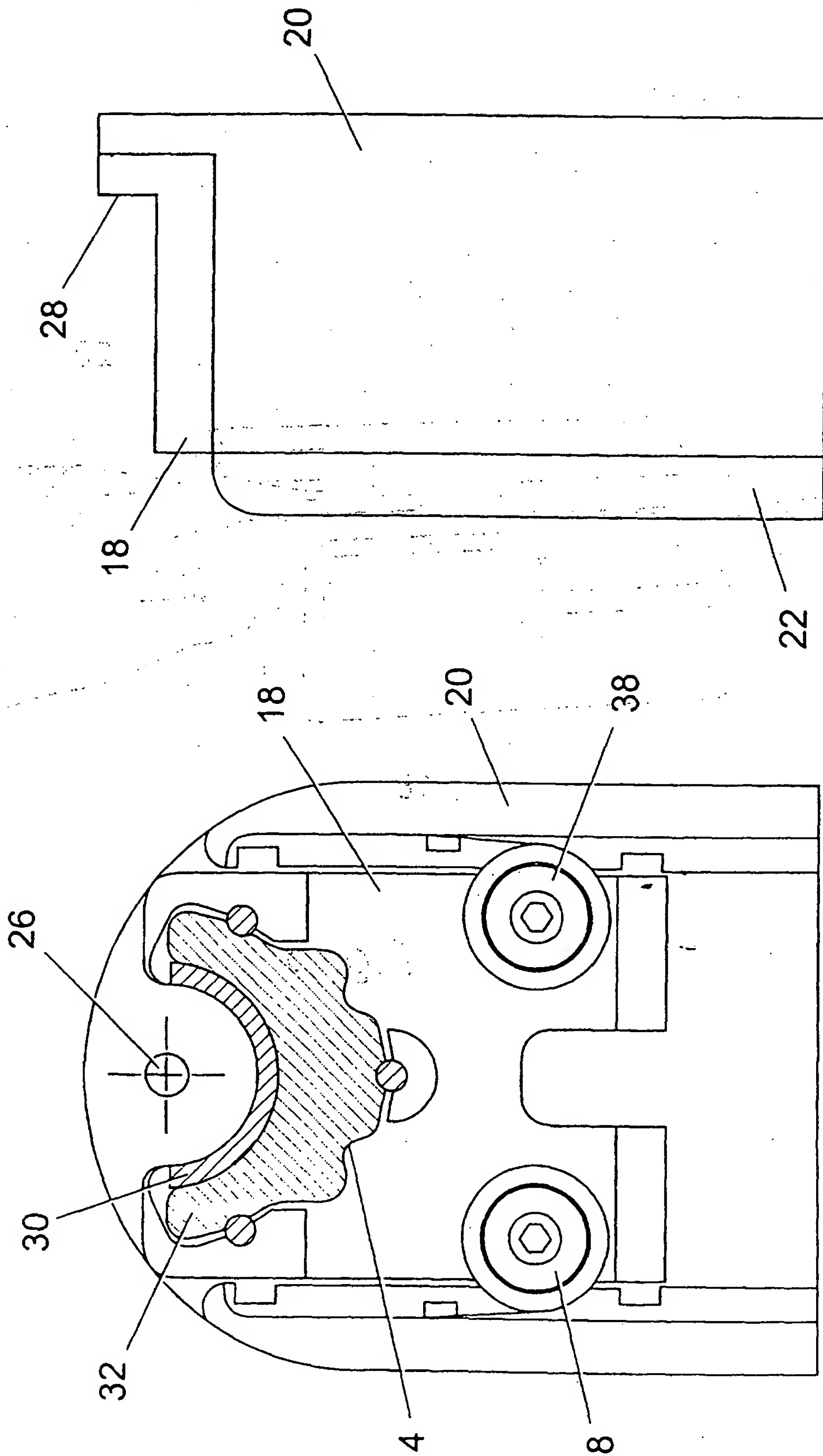
20

28

18

22

*Fig. 4*

18

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4

8

*Fig. 3*

Fig. 5

54

52

56

*Fig. 6*

64

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66

68

*Fig. 7*

72    74

70

76

*Fig. 8a*

72

70

74

78

*Fig. 8b*

84    80    82

84

*Fig. 9*

92

91

89

90

88

87

Fig. 10

Fig. 11

*Fig. 12*

111

109

108

106

110

107

105

Fig. 13

Fig. 13a

120 — | 120 mg/dl | — 121

119

118

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114

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116

113

112

Fig. 14

Fig. 15

128

130

129
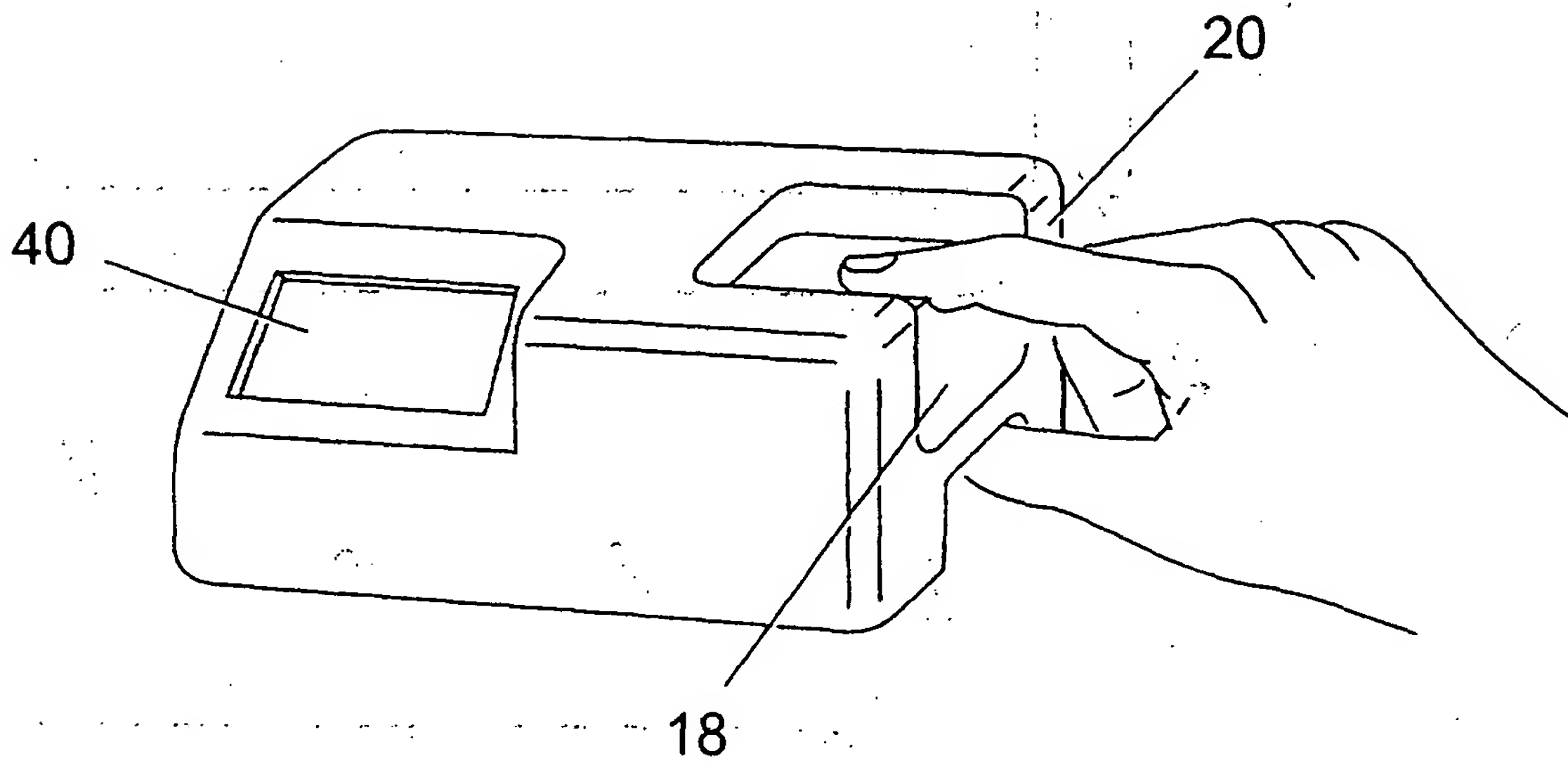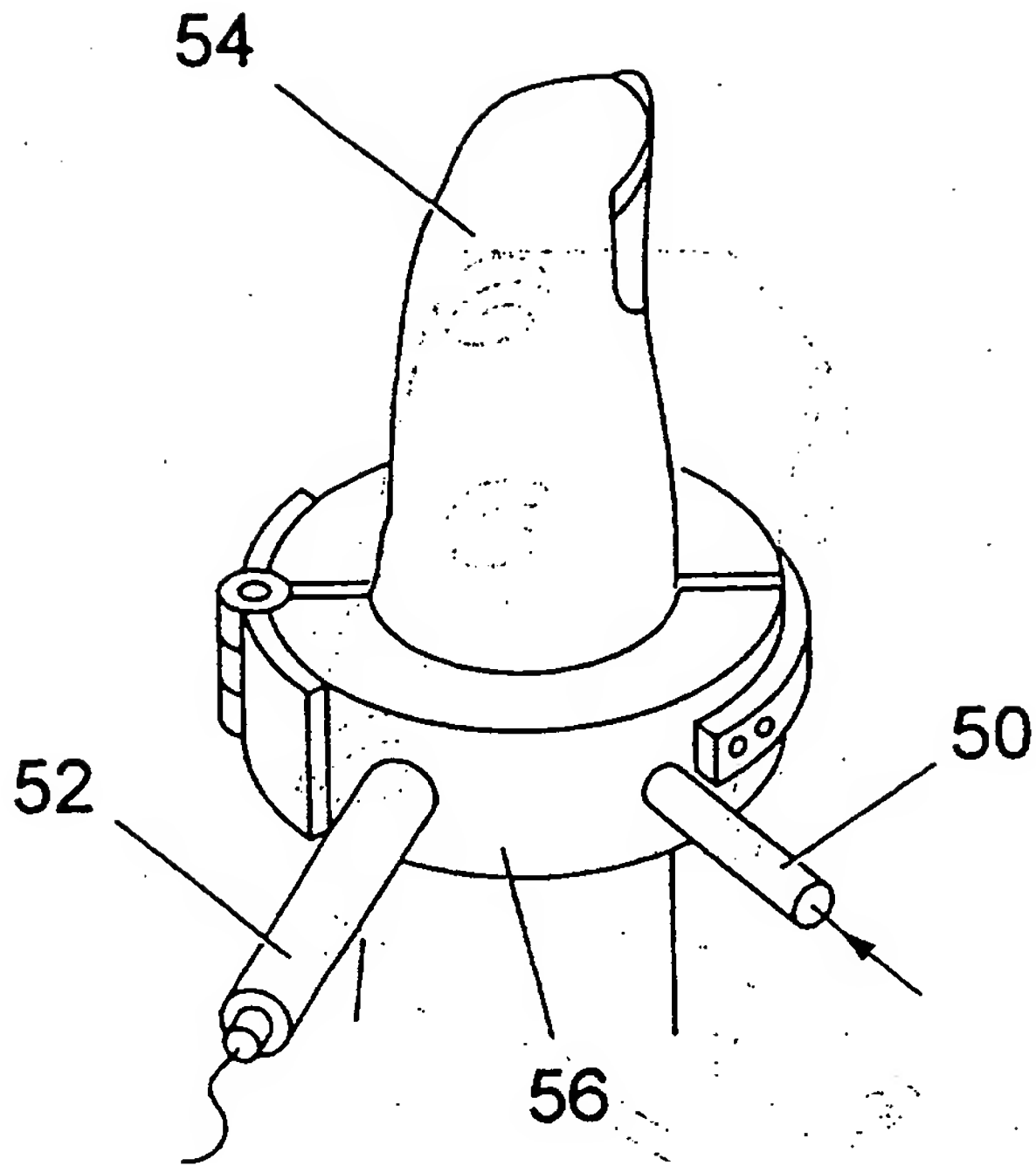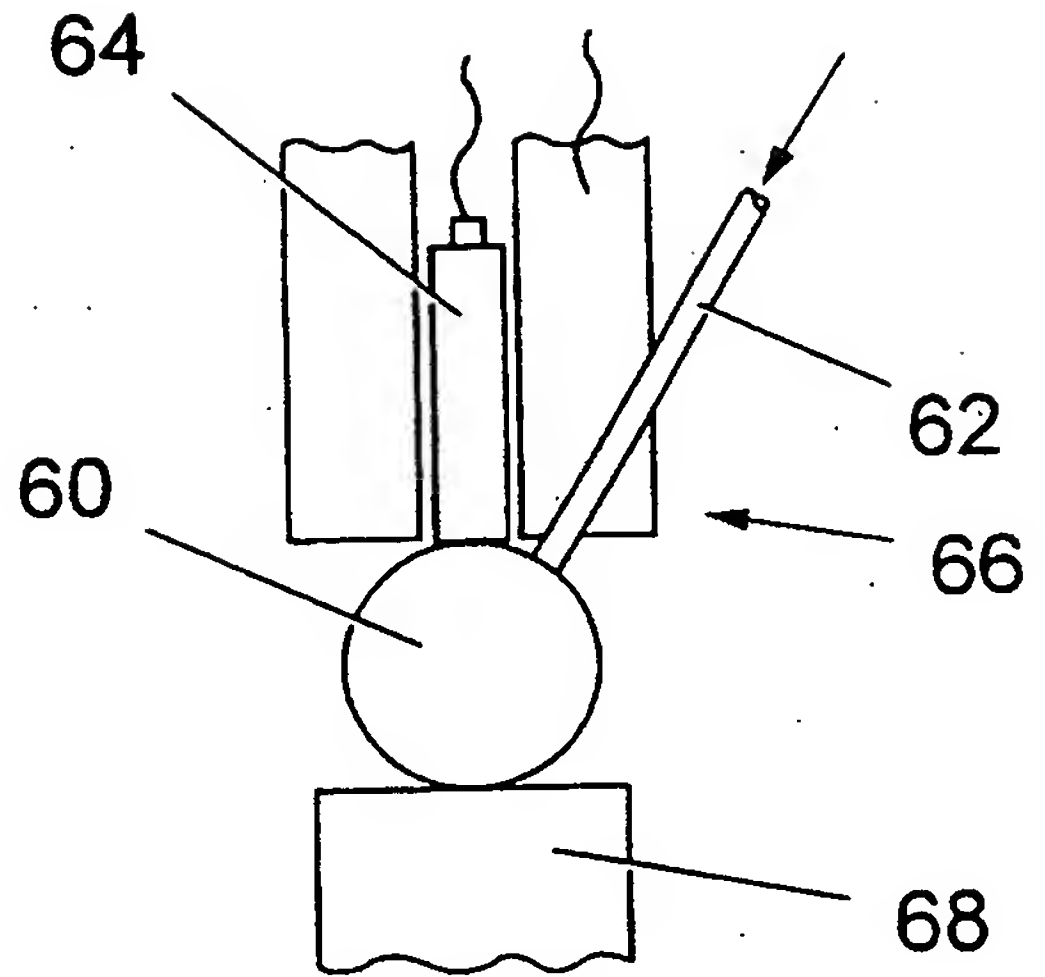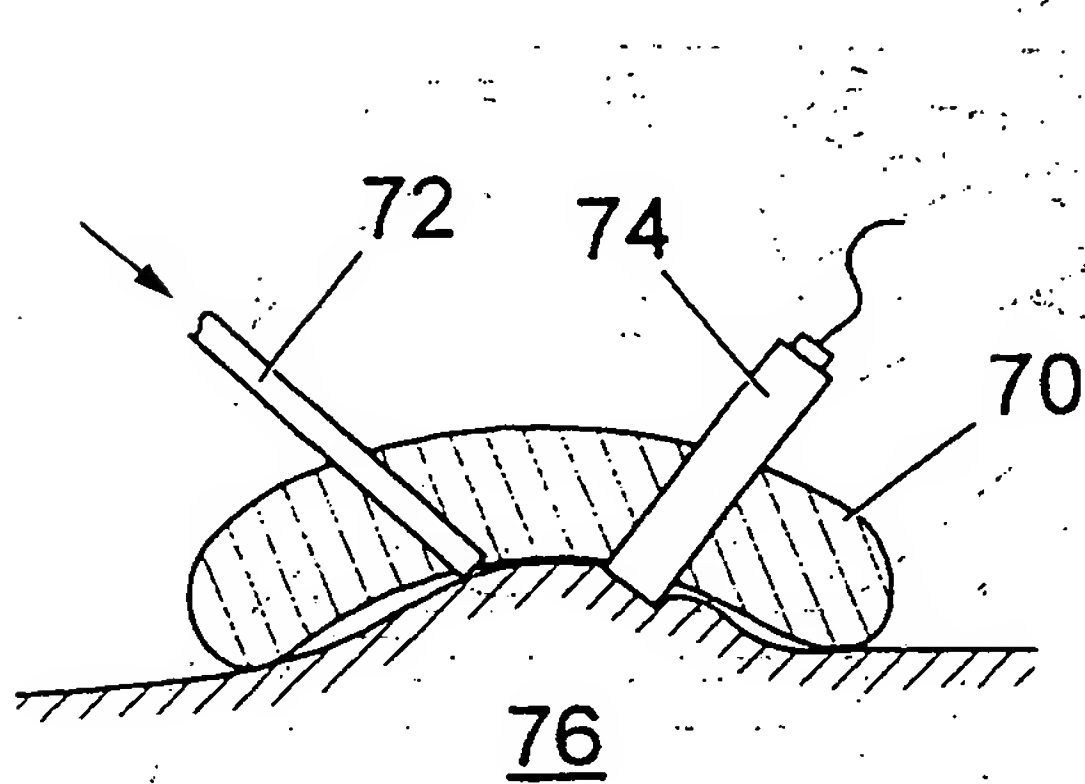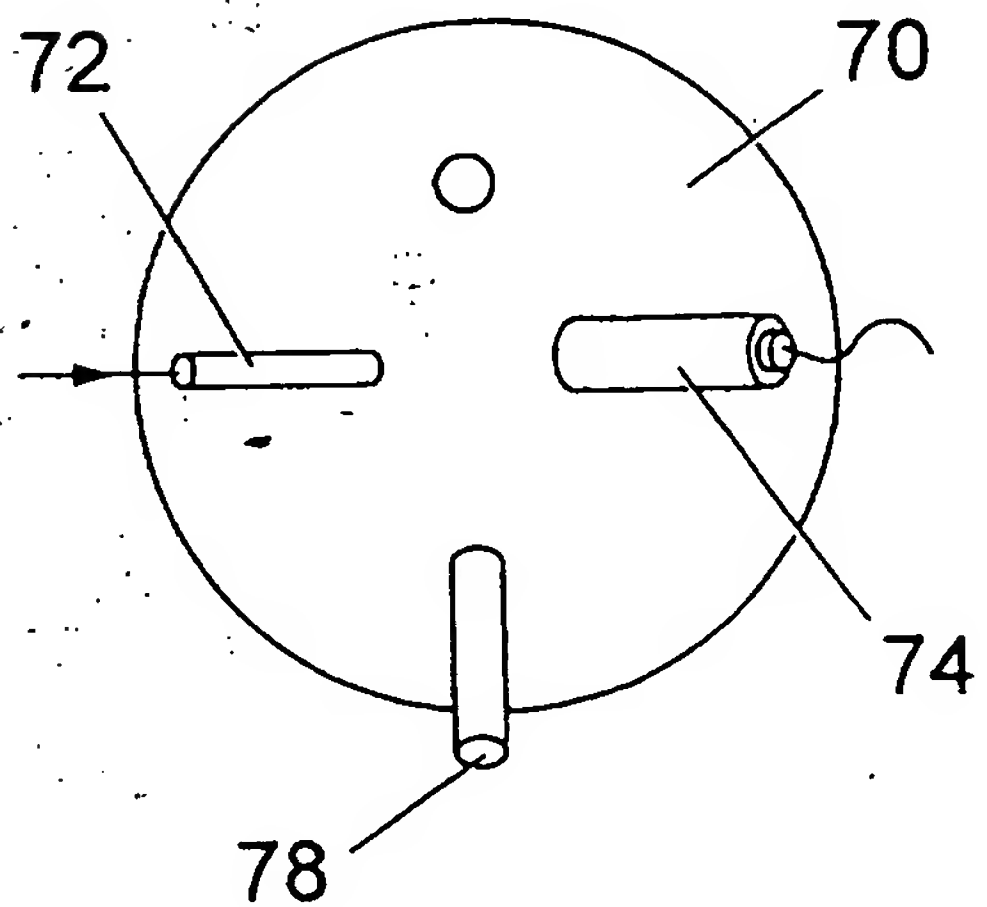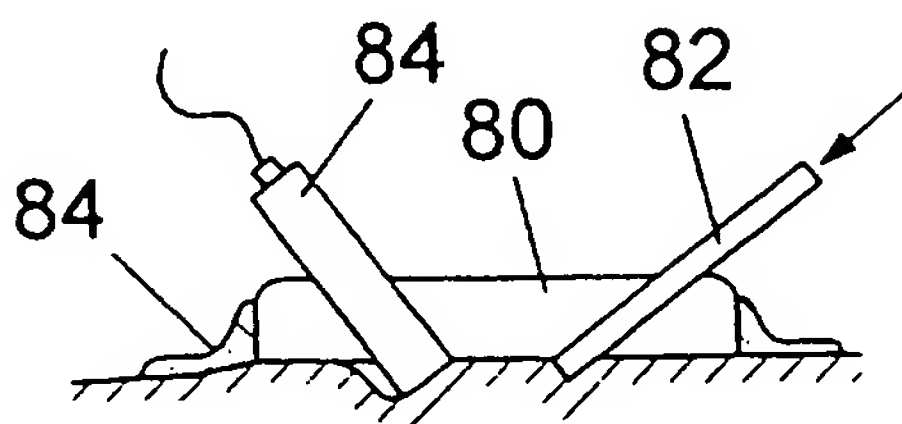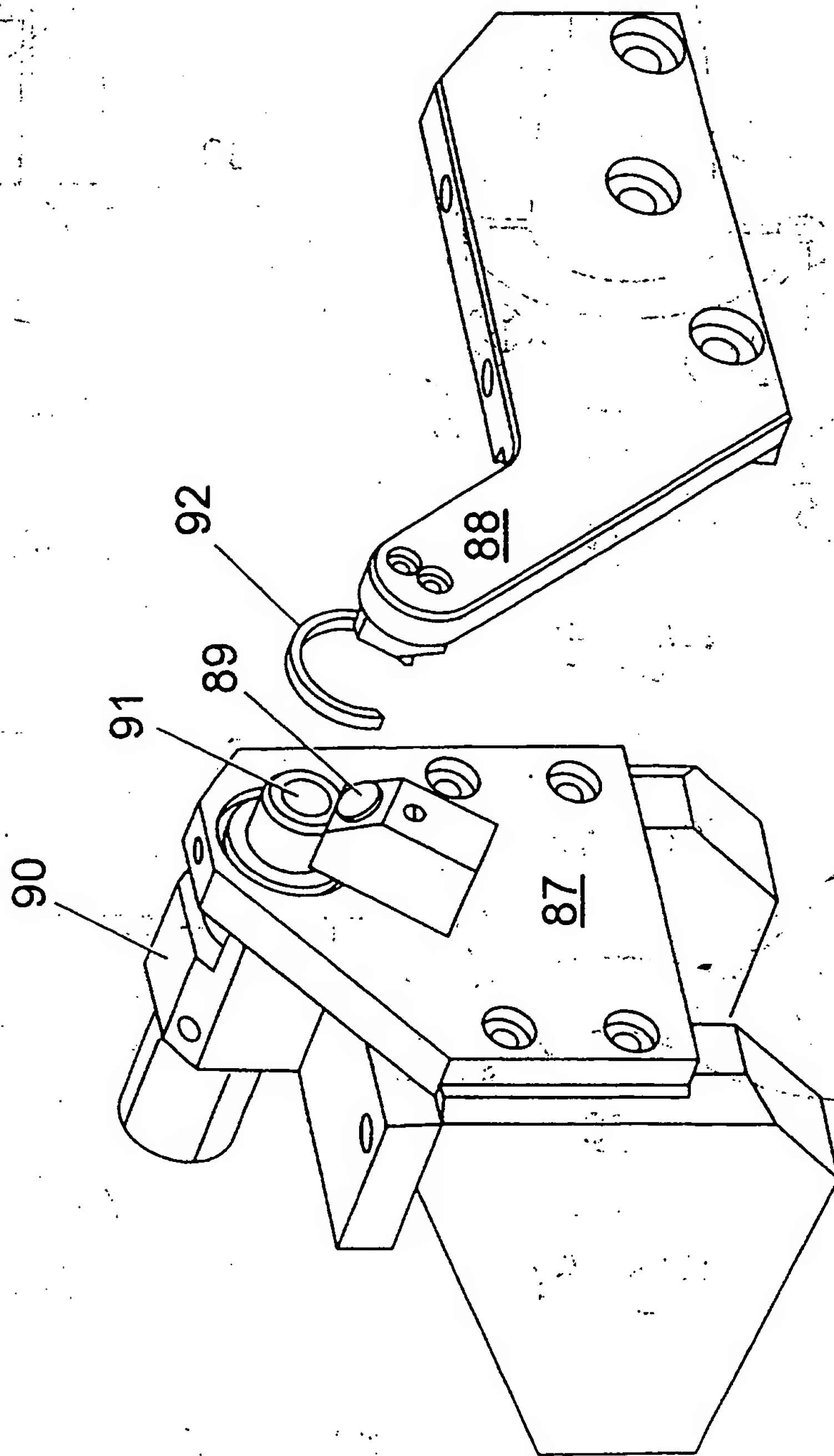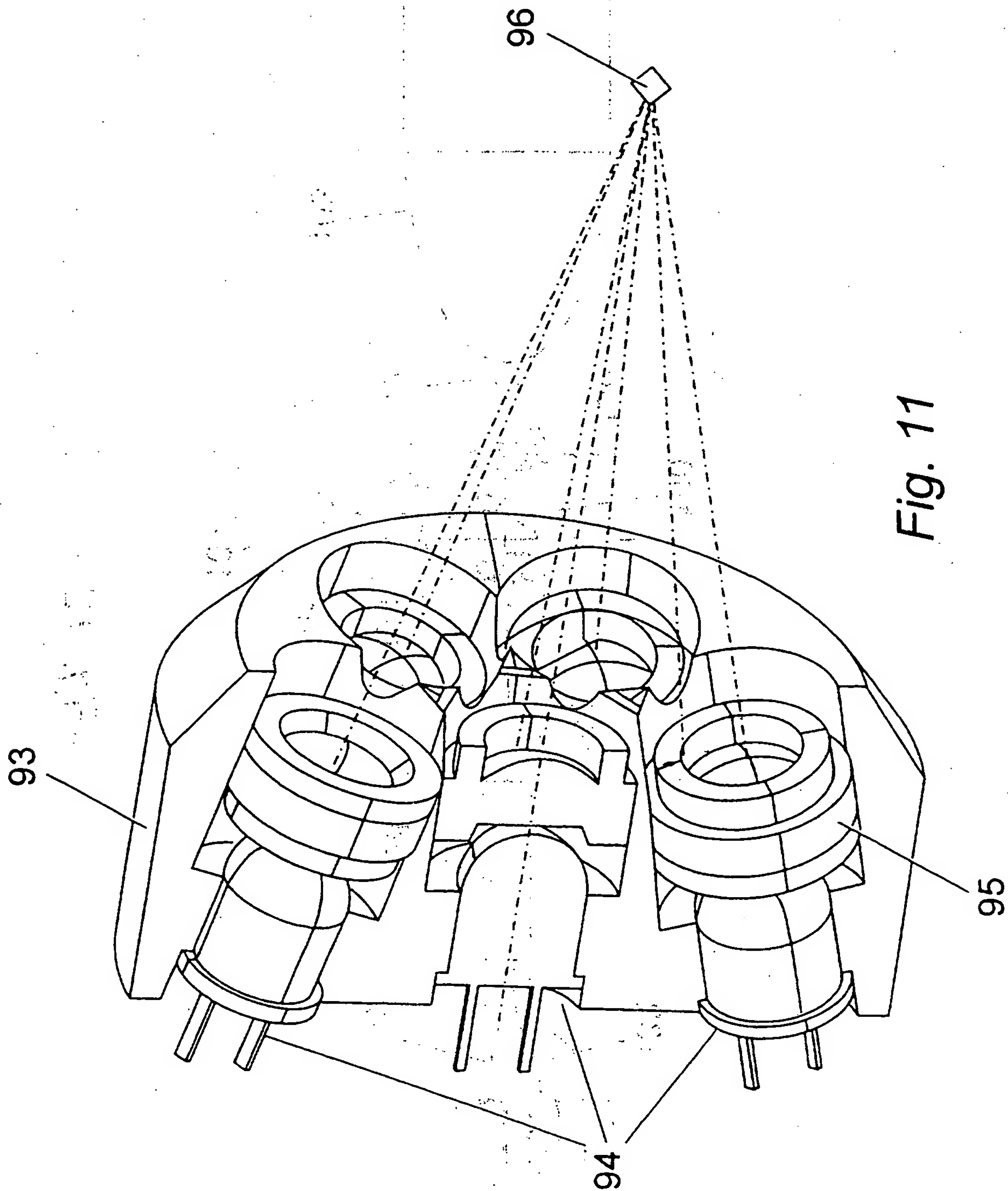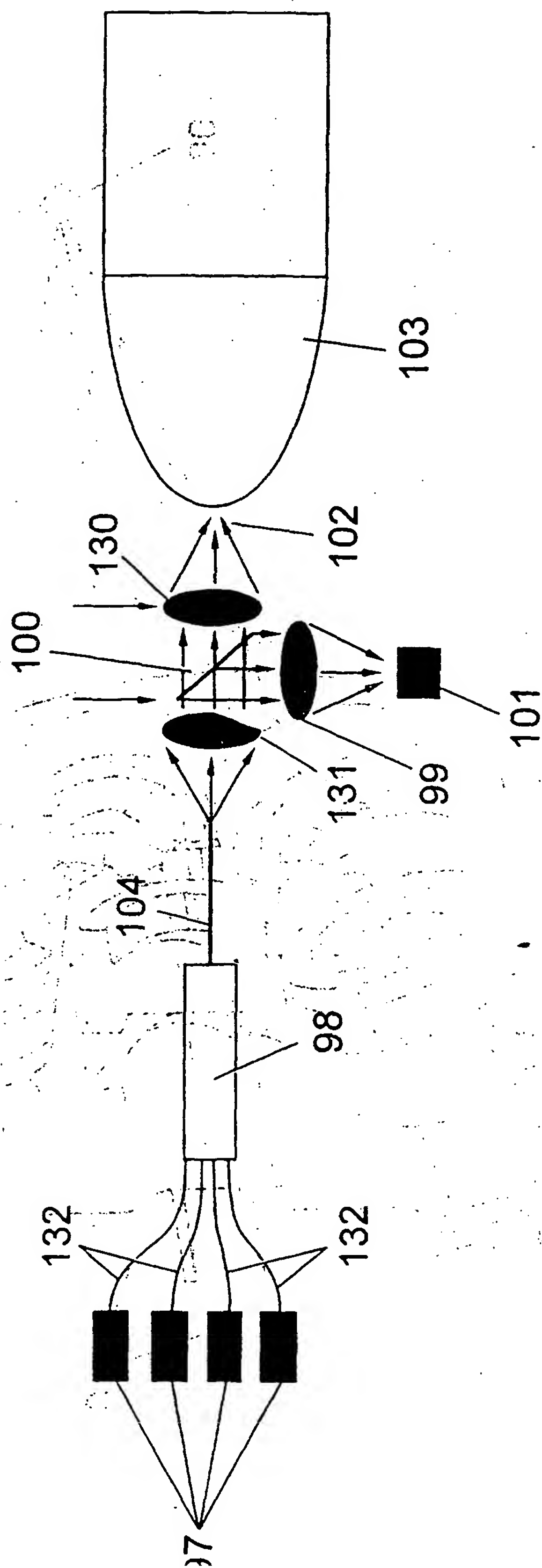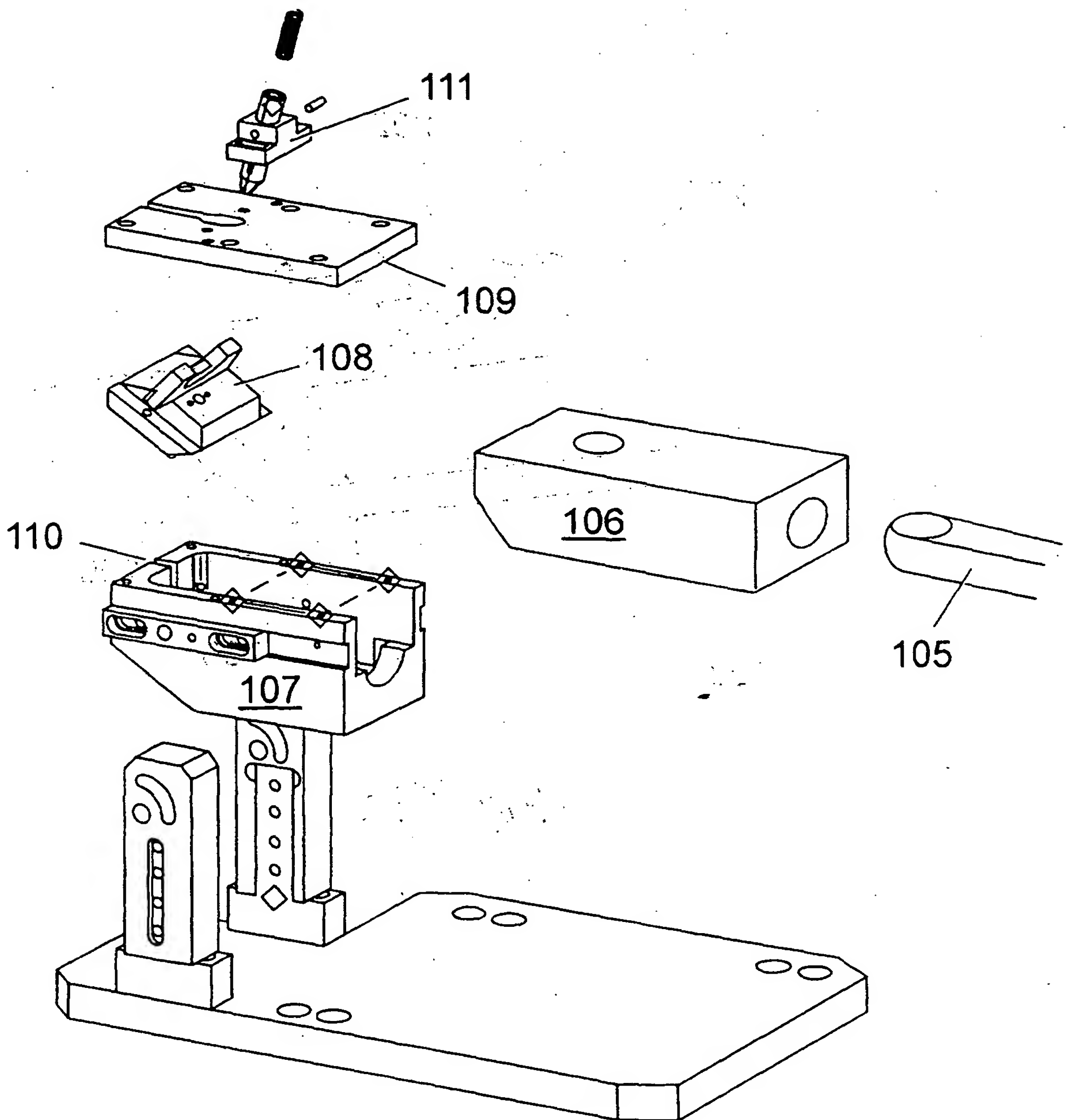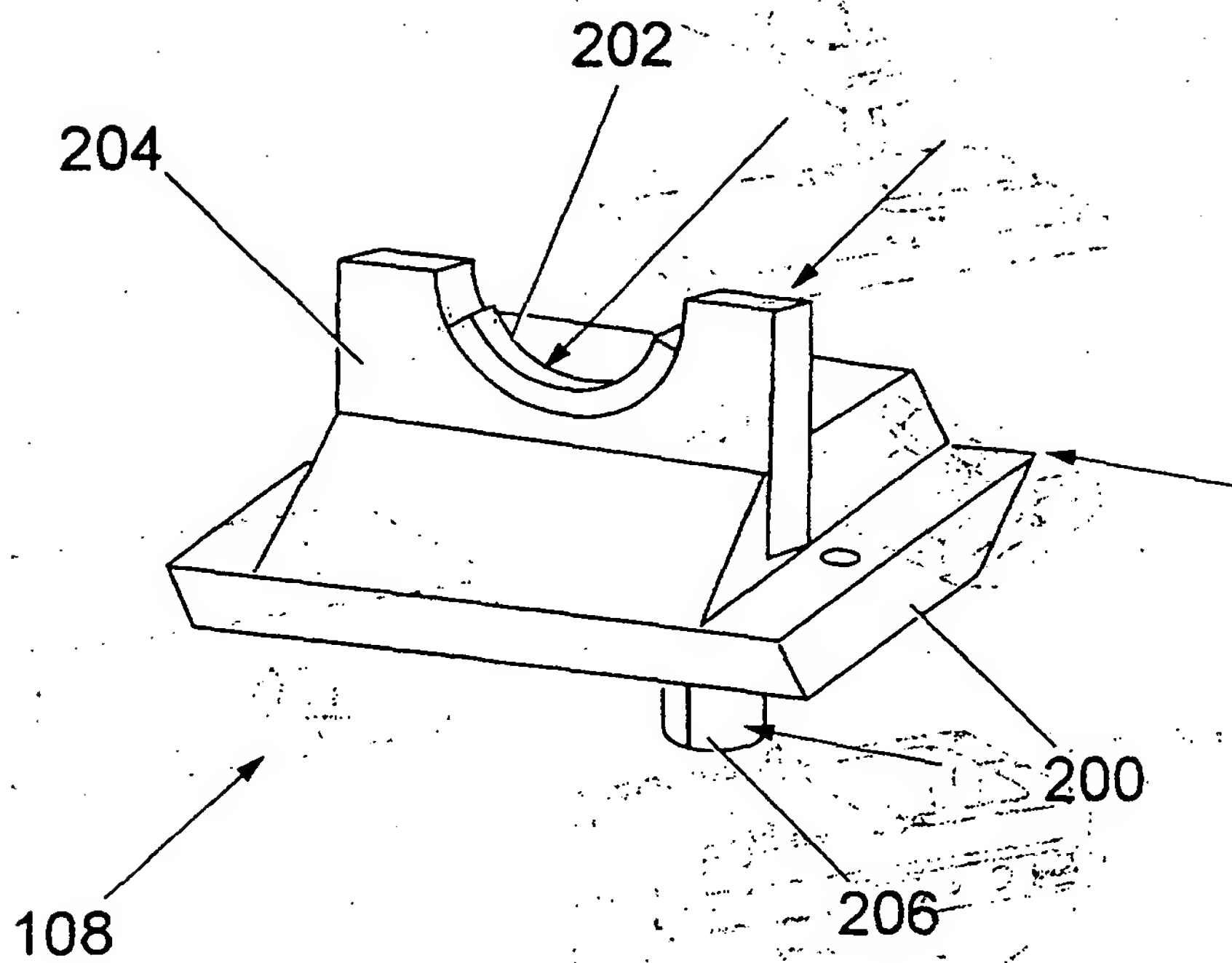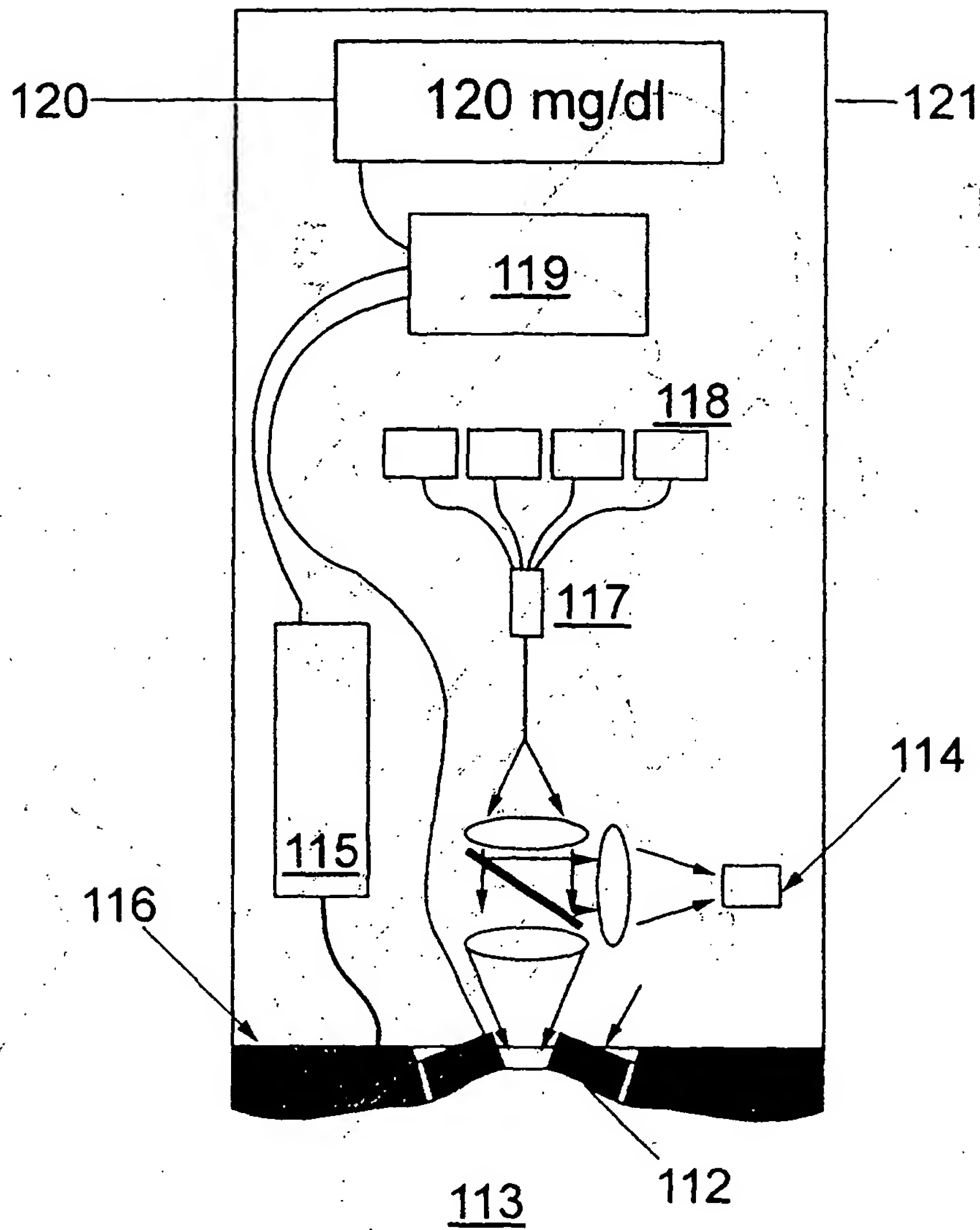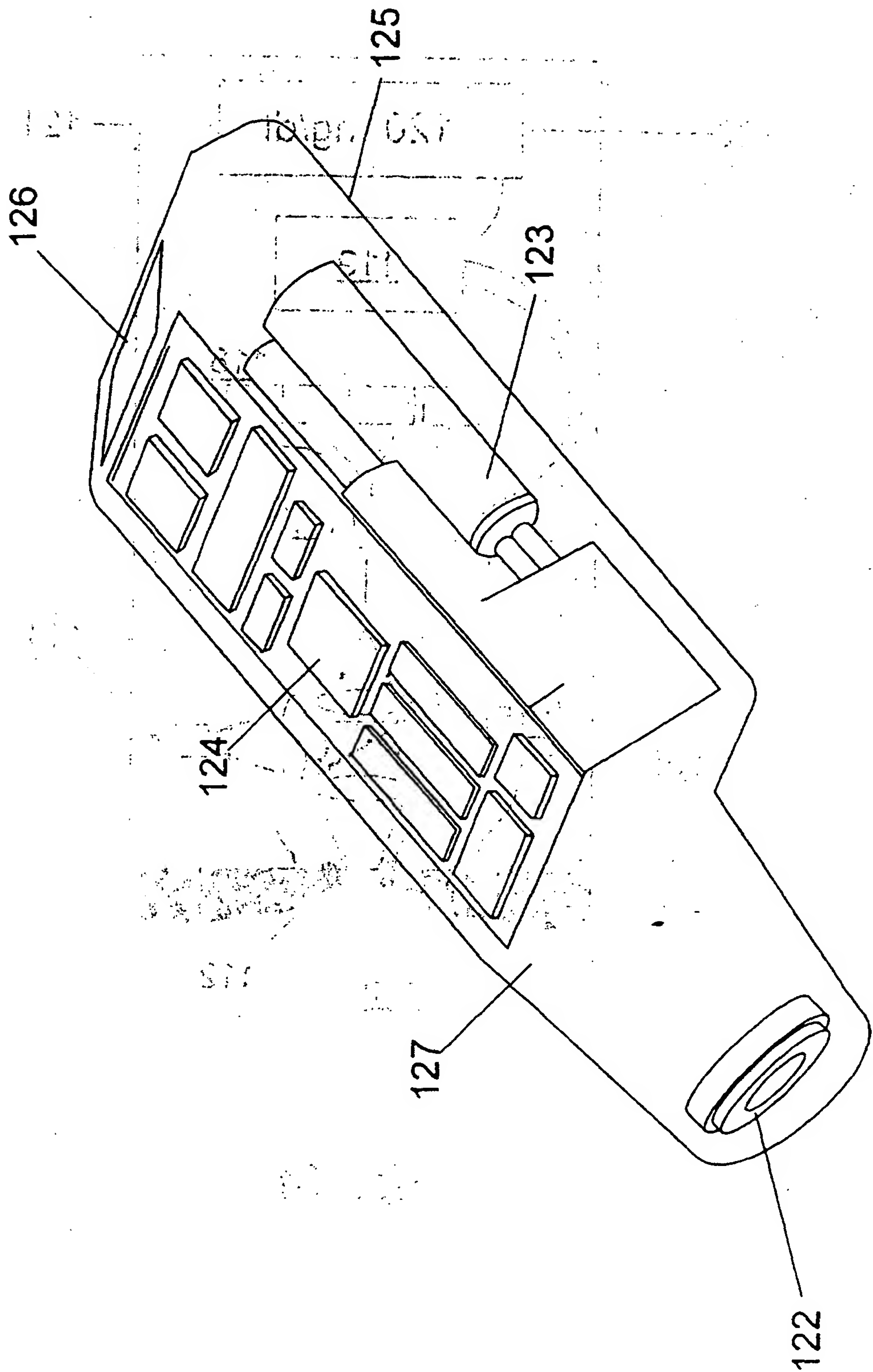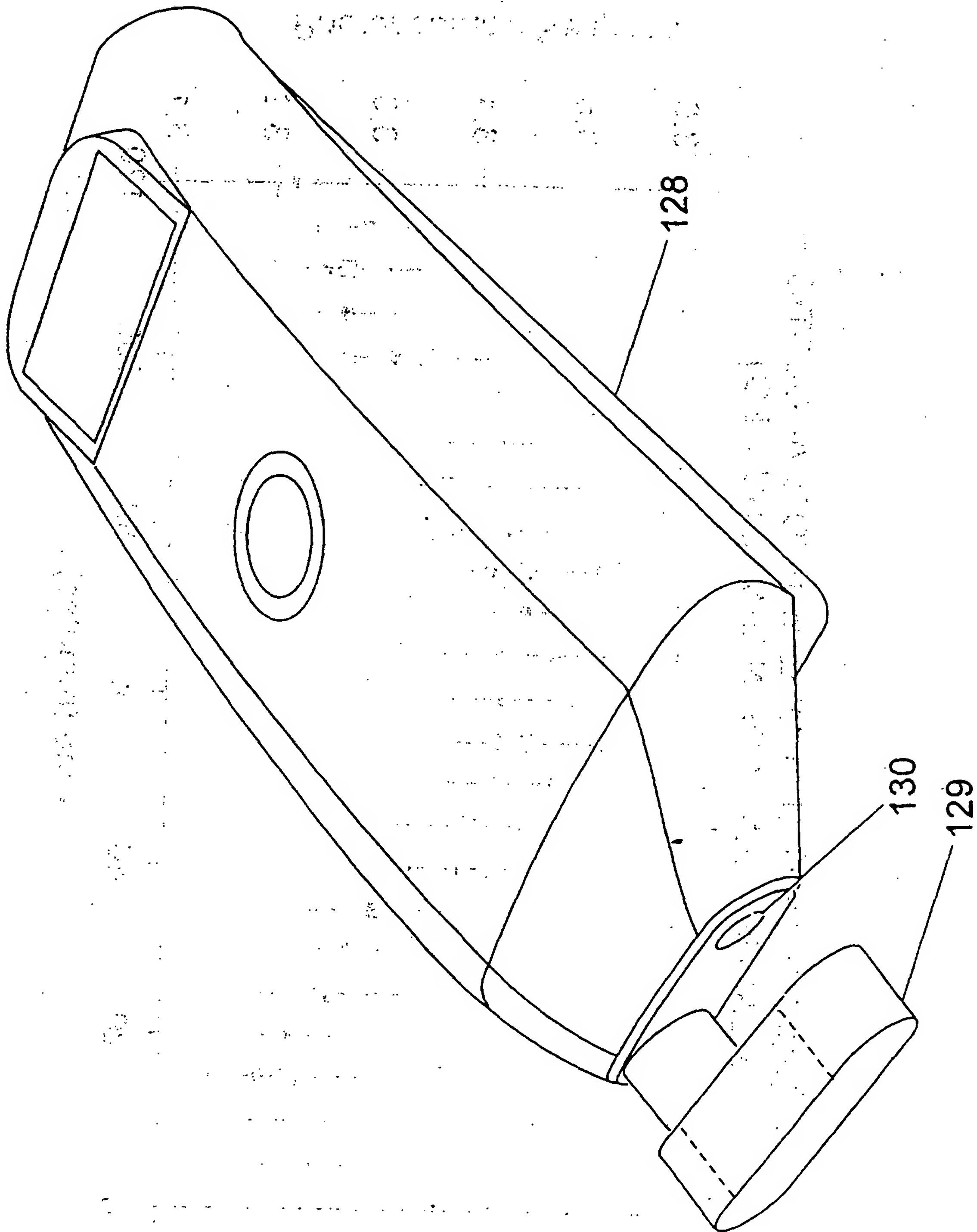
Fig. 16

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC
MEASUREMENT FOR NORMAL SUBJECT

Photoacoustic Responce
(volts)

Clinical Blood Glucose
Concentration (mmol/l)

Time (minutes)
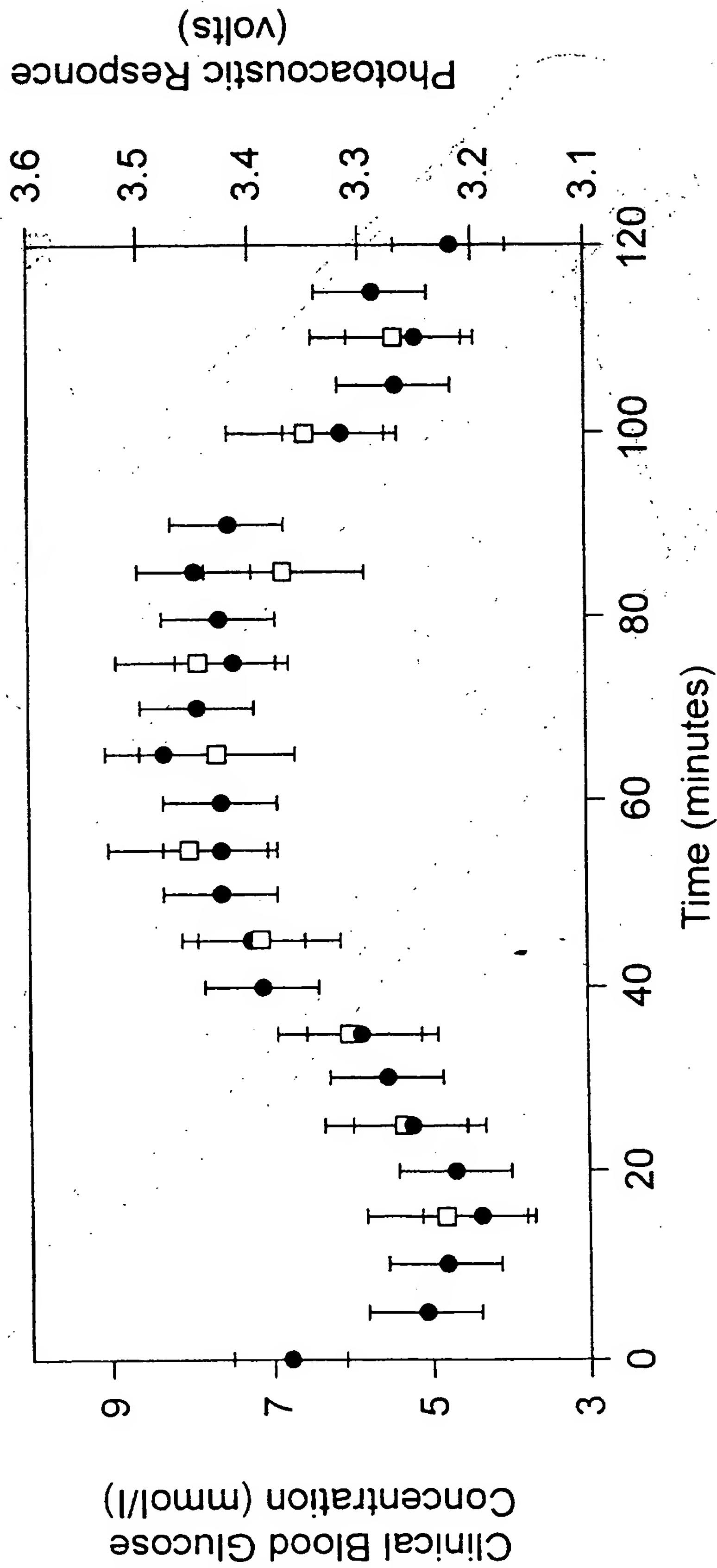
Fig. 17

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC
MEASUREMENT FOR TYPE 1 DIABETIC

Photoacoustic Response
(Volts)

Time (minutes)

Concentration (mmol/l)
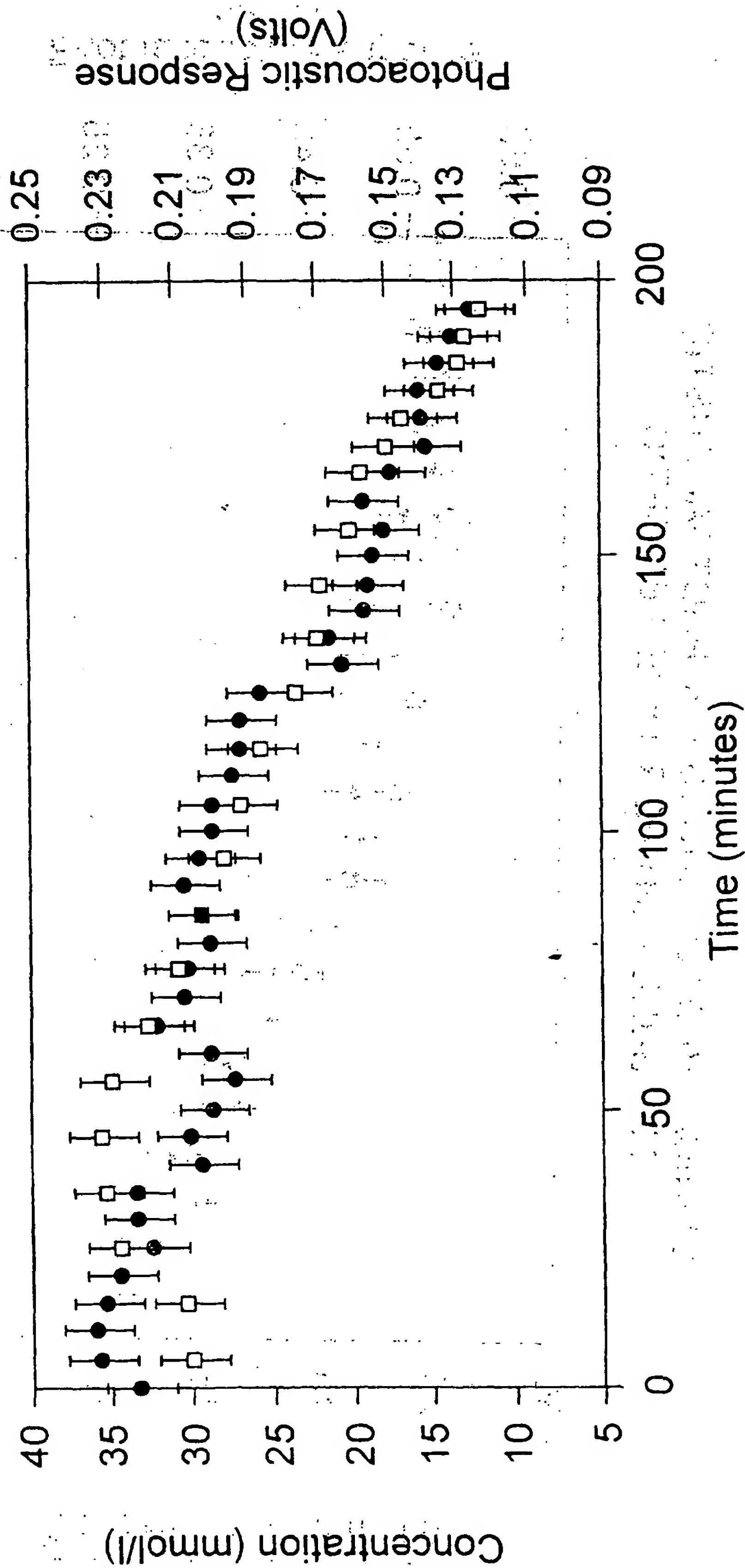
Fig. 18

CLINICAL BLOOD GLUCOSE vs. PHOTOACOUSTIC
MEASUREMENT FOR TYPE 2 DIABETIC
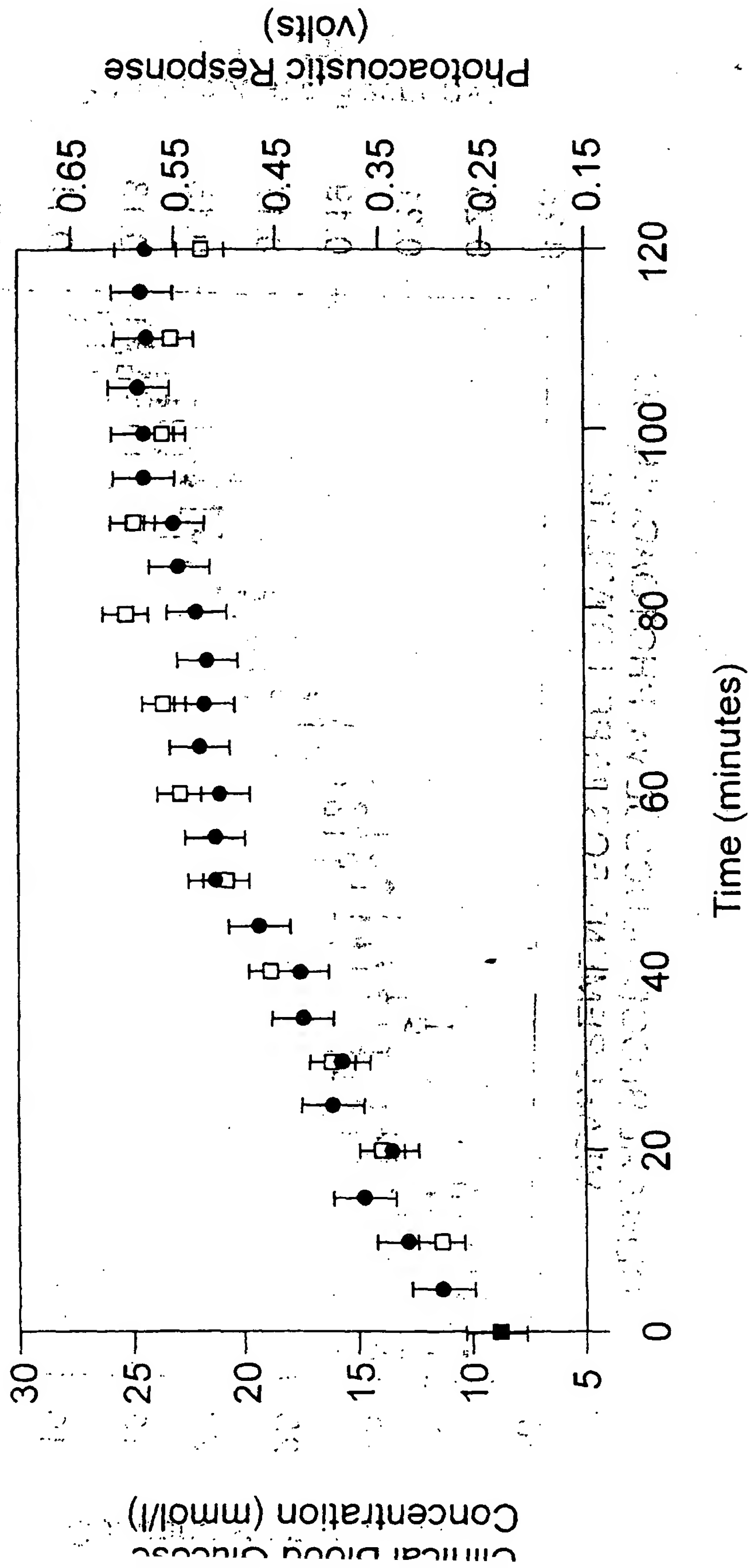


*Fig. 19*

1  Biological Measurement System

2

3  This invention relates to apparatus for use in non-

4  invasive in vivo monitoring of physiological substances

5  such as blood and the like.

6

7  One particular, but not exclusive, application of the

8  present invention is in the monitoring of blood

9  glucose, for example in the management of diabetes

10  mellitus.  It is accepted that the management of

11  diabetes can be much improved by routine monitoring of

12  blood glucose concentration and clinicians suggest that

13  monitoring as often as four times per day is desirable.

14

15  The monitoring technique currently available for use by

16  patients involves using a spring loaded lancet to stab

17  the finger to obtain a blood sample which is

18  transferred to a glucose test strip.  The concentration

19  is derived either by reading the test strip with a

20  reflectance meter or by visual comparison of colour

21  change against a colour scale.  Many diabetics find the

22  testing onerous as the technique is painful,

23  inconvenient, messy, potentially embarrassing and

24  offers a site for the transmittance and acceptance of

25  infection.

1    Techniques have also been developed for non invasive

2    measurement using transmittance or reflectance

3    spectroscopy.   However the required instruments are

4    expensive and it is difficult to obtain accurate and

5    repeatable measurements.

6

7    There are also known various types of in vivo chemical

8    sensors.   These rely on implanting minimally invasive

9    sensors under the skin surface, but such sensors have

10   poor long term reproducibility and bio-compatibility

11   problems.

12

13   There is therefore a need for improved means for

14   routine monitoring of blood glucose in a manner which

15   is simple and straightforward to use.

16

17   The present invention makes use of photoacoustic

18   techniques.   The fundamentals of photoacoustic

19   techniques are well known per se.   A pulse of light,

20   typically laser light, is applied to a substance

21   containing an analyte of interest in solution or

22   dispersion, the wavelength of the applied light being

23   chosen to interact with the analyte.   Absorption of the

24   light energy by the analyte gives rise to microscopic

25   localised heating which generates an acoustic wave

26   which can be detected by an acoustic sensor.   These

27   techniques have been used to measure physiological

28   parameters in vitro.

29

30   US Patents 5348002 and 5348003 (Caro) propose the use

31   of photoacoustics in combination with photoabsorption

32   for the measurement of blood components in vivo.

33   However, the arrangement proposed by Caro has not been

34   demonstrated as a workable system and may suffer from

35   interference to a degree which would preclude useful

36   acoustic signals, and since they would also suffer from

1 interference and resonance effects from hard structures

2 such as bone.

3

4 It has also been proposed by Poulet and Chambron in

5 Medical and Biological Engineering and Computing,

6 November 1985, Page 585 to use a photoacoustic

7 spectrometer in a cell arrangement to measure

8 characteristics of cutaneous tissue, but the apparatus

9 described would not be suitable for measuring blood

10 analytes.

11

12 Published European Patent Application 0282234A1

13 (Dowling) proposes the use of photoacoustic

14 spectroscopy for the measurement of blood analytes such

15 as blood glucose. This disclosure however does not

16 show or suggest any means which would permit the

17 required degree of coupling to body tissues for use in

18 vivo.

19

20 Accordingly, the present invention provides a sensor

21 head for use in photoacoustic in vivo measurement,

22 comprising a housing shaped to engage a selected body

23 part, light transmission means terminating in said

24 housing so as to transmit light energy from a light

25 source to enter the body part along a beam axis, and

26 acoustic transducer means mounted in the housing to

27 receive acoustic waves generated by photoacoustic

28 interaction within the body part, the acoustic

29 transducer means being disposed in the housing to

30 receive said acoustic wave in a direction of high

31 acoustic energy.

32

33 The expression "direction of high acoustic energy" is

34 used herein to denote a direction other than the

35 forward direction of the light beam. Preferably, the

36 transducer means is disposed so as to intercept

1  acoustic energy propagating at right angles to the

2  optical beam axis, or at an angle to the optical beam

3  axis which may be down to about 20°, typically about

4  45°.

5

6  An exact measure of the angle of high acoustic energy

7  can be worked out but is dependent upon the specific

8  geometry of the light source, the properties of the

9  tissue and the absorption coefficient of the tissue.

10  One model for understanding the propagation of the

11  acoustic energy in any homogenous media was developed

12  by Huyghens and is called the principle of

13  superposition.  In this model each volume element that

14  is illuminated by the light generates an acoustic

15  pressure wave that radiates outward in a spherical

16  manor.  The magnitude of the pressure wave at each

17  volume element depends on the intensity of the optical

18  beam at that location, the absorption coefficient of

19  the material at that location, the wavelength of light

20  and on several other physical properties of the

21  material such as the speed of sound and the specific

22  heat.  The signal measured at the detector is just the

23  superposition of all pressure waves from all points

24  that are illuminated by the source light.  An

25  analytical solution for the pressure wave has been

26  worked out for a few cases in aqueous material.  The

27  analytical case that best matches the in-vivo

28  measurements is that of a cylindrical optical beam

29  propagating in a weekly absorbing material.  In this

30  case the direction of highest acoustic energy is

31  perpendicular to the optical axis.  The base detector

32  location is with the plane of the detector

33  perpendicular to the acoustic energy, or parallel to

34  the optical axis.  This is because the acoustic

35  detector has the highest sensitivity when the acoustic

36  energy strikes the detector perpendicular to the plane

1     of the detector. This analytical model is not

2     completely accurate for the in-vivo measurement case

3     because of scattering of the tissue and because the

4     tissue absorbs more than the model predicts. These

5     differences indicate that a different position for the

6     detector will be optimal. A detailed numeric model is

7     required to determine the best detector location and is

8     dependent upon the beam properties (focused to a point,

9     colligated, etc.), body site (finger, earlobe, arm

10    etc.) and wavelength. One skilled in the art can

11    readily develop an appropriate mode. However, suitable

12    locations for a detector will generally be at an angle

13    to the optical axis. Angles between 40 and 90 degrees

14    should be suitable.

15

16    In one preferred arrangement, the acoustic transducer

17    means is arranged parallel to the optical beam axis.

18    This arrangement is particularly suitable for use where

19    the selected body part is the distal portion of a

20    finger, in which case the housing may include a

21    generally half-cylindrical depression in which the

22    finger may be placed with the light transmission means

23    aimed at the end of the finger.

24

25    Preferably, the acoustic transducer means comprises a

26    piezoelectric transducer which most preferably is of a

27    semi-cylindrical shape. This transducer may be

28    provided with a backing of lead or other dense

29    material, and the backing may have a rear surface

30    shaped to minimise internal acoustic reflection.

31

32    Alternative transducer means include a capacitor-type

33    detector, which is preferably small and disk-shaped; an

34    integrated semiconductor pressure sensor; and an

35    optical pressure sensor, for example based on an

36    optical fibre.

1　In an alternative arrangement, the plane of the
2　transducer may be arranged to be perpendicular to the
3　optical axis to detect the acoustic wave which is
4　propagating in a direction opposite to the direction of
5　the light beam.  For example, the acoustic transducer
6　means may be part-spherical with an aperture to allow
7　access for the light beam.  This may be particularly
8　suitable for engagement with a body part other than the
9　finger, for example the back of the arm.
10
11　The generation of a surface acoustic wave is an
12　inherent aspect of the in vivo pulsed photoacoustic
13　generation in tissue and may be used to characterize
14　tissue properties such as density.  A surface wave
15　detector may be provided in the sensing head assembly.
16
17　Preferably means are provided for ensuring a consistent
18　contact pressure between the selected body part and the
19　acoustic transducer means.  In the case where the
20　selected part is the distal portion of the finger, said
21　means may be provided by mounting the portion of the
22　housing engaged by the finger in a resiliently biased
23　fashion against the remainder of the housing, and
24　providing means to ensure that measurement is effected
25　when the predetermined force or pressure is applied by
26　the subject against the resilient bias.  In the case
27　where the selected part is the earlobe, said means may
28　be provided by placing the ear between two plates and
29　applying pressure to the ear with springs or weights or
30　other force method.  The two plates holding the ear may
31　contain a removable insert.  The two plates may be flat
32　or may be of another shape to optimally position the
33　detector with respect to the beam axis.
34
35　In addition, the present invention provides a sensor
36　head for use in photoacoustic in-vivo measurements,

1     comprising a housing shaped to receive a removable

2     insert, a removable insert that engages a selected body

3     part, the insert being fitted to an individual,

4     allowing for a range of sizes of body parts to be used,

5     and further comprising light transmission means

6     terminating in or near said removable insert so as to

7     transmit light energy from a light source or sources to

8     enter the body part along a beam axis, and an acoustic

9     transducer means mounted in the housing or in the

10    removable insert to receive acoustic waves generated by

11    photoacoustic interaction within the body part to

12    receive said acoustic waves in a direction of high

13    acoustic energy.

14

15    From another aspect the present invention provides an

16    in vivo measuring system comprising a sensor head as

17    hereinbefore defined in combination with a light source

18    coupled with the light transmission means, and signal

19    processing means connected to receive the output of the

20    acoustic transducer means and to derive therefrom  a

21    measurement of a selected physiological parameter.

22

23    Preferably, the light transmission means is a fiber

24    distribution system where each light source is

25    connected to an individual fiber and when multiple

26    light sources are used the multiple fibres are joined

27    by some standard fiber combining method, such as a

28    wavelength division multiplexer or a fiber coupler.

29    The fiber that comes from the light source, or contains

30    the combined light for a multiple source system, is

31    then terminated in proximity to the body part being

32    measured.  The fiber could be in contact with the body

33    part or alternatively standard optics, such as lenses,

34    beamsplitters and such, could be employed to convey the

35    light from the end of the fiber to the body part.  A

36    reference detector or several reference detectors and

1     beamsplitters can be added to the optical distribution

2     system to determine the energy of the light entering

3     the body part.

4

5     Alternatively, the optical distribution system may

6     contain mechanical holders, lenses and such to convey

7     the light from the source, or sources, to a location in

8     proximity to the body part being measured. A reference

9     detector or several reference detectors and

10    beamsplitters can be added to the optical distribution

11    system to determine the energy of the light entering

12    the body part.

13

14    The acoustic signal from the detector contains

15    information in both time and frequency, and there may

16    be information from several sources. The processing

17    means is preferably a multi-dimensional processing

18    method, such as Classical Least Squares (CLS) or

19    Partial Least Squares (PLS). Alternatively the

20    processing method may be more flexible, such as a

21    Neural Network. In addition to these methods the

22    signals may be analysed for their frequency content

23    using such techniques as Fourier Analysis or Frequency

24    Filtering In addition techniques may be employed that

25    use time information such as the time delay from source

26    trigger. Techniques that combine both frequency and

27    time information may be employed, such as Wavelet

28    analysis.

29

30    The light source is preferably a laser light source and

31    is most suitably a pulsed diode laser, but may utilise

32    a set of such lasers or utilise a tunable laser source.

33    In a particularly preferred form, suitable for use in

34    measuring blood glucose concentration, a laser diode is

35    used with a wave length in the range of approximately

36    600 nm to 10,000 nm and a pulse duration of the order

1  of 5 to 500 ns.

2

3  The delivery to the measurement site may be either

4  directly or by optical fibre with a suitable optical

5  element to focus the beam into the tissue.

6

7  Preferably means are provided for time multiplexing

8  multiple sources when multiple sources are used. Each

9  source is switched on, and it generates an optical

10  pulse, or a set of optical pulses. This pulse, or set

11  of pulses, generates an acoustic signal that is

12  detected by the detector. Each source is pulsed in

13  sequence until all sources have been used to generate

14  their own signal.

15

16  The measuring system may conveniently be in the form of

17  a self contained system including a power supply and a

18  readout, which may be carried on the person and used at

19  any convenient time.

20

21  It is also possible for such a self contained system to

22  incorporate, or to be provided with facilities for

23  connection to, a cellular telephone, two-way pager or

24  other communication device for routine transmission of

25  measurements taken to a central data collection point.

26

27  In addition the measuring system may have provision for

28  manipulating the body part under measurement and for

29  performing additional measurement of the tissue to get

30  other information about the state of the physiology of

31  the issue. It is well-known in the art that squeezing

32  a section of tissue to increase the pressure and then

33  releasing the pressure will cause changes in the total

34  blood volume in the measurement site. The present

35  invention may allow for this type of manipulation

36  including the squeezing of a body part, such as an

earlobe, and making photo acoustic measurements at
several different pressures.  The present invention may
also allow for the measurement of the temperature of
the body site and to apply a correction to the
measurements based upon the temperature of the body
site.

Another type of physiological manipulation is body
temperature.  It is known in the art that several
parameters involved in the detection of the photo
acoustic signal, such as the speed of sound, are
dependent upon the temperature of the medium the signal
is propagating through (the tissue).  Also the
profusion of the blood in the small capillaries is
dependent upon the temperature of the tissue.
Additional information about the tissue can be obtained
if the photo acoustic measurement is made at several
temperatures, both higher and lower than ambient
temperature.  This additional information is used to
better eliminate interferences to the determination of
the analyte under investigation.  These are only two
examples of manipulating the body site and are not
intended to be an exhaustive list, and they can be used
in combination with other manipulation techniques.

The in-vivo measuring system may comprise a means for
storing calibration coefficients or operation
parameters or both calibration coefficients and
operational parameters, in order to calibrate the
instrument and to set critical operational parameters.

Another aspect of the present invention provides a
means for adjusting the calibration coefficients and
operational parameters to be specific to a particular
person and may be used to adjust for such things as
body part size, skin color, skin condition, amount of

1 body fat, efficiency of the detector and efficiency of

2 the source(s).

3

4 In addition the present invention may provide for

5 having the specific calibration coefficients and

6 operational parameters be contained in a storage site

7 located in the removable insert. This allows for the

8 system to be both mechanically and operationally

9 configured to a particular individual. Additionally

10 the invention may allow for the calibration

11 coefficients and operational parameters to be stored in

12 two locations, one in the non-removable housing and one

13 in the removable insert with some of the coefficients

14 and parameters stored in each location. This allows

15 for reader system coefficients to be stored in the

16 reader and coefficients specific to an individual to be

17 stored in the removable insert for that person,

18 enabling many people to use the same reader.

19

20 Another aspect of the present invention provides means

21 for connecting the non-invasive measuring system to an

22 invasive measuring system for the purpose of

23 calibrating or adjusting the operational parameters of

24 the non-invasive measuring system. Such connection may

25 be accomplished, but is not limited to, communication

26 by a wire, IR link or radio waves.

27

28 Another aspect of the present invention provides a

29 method for removing instrument drift from the

30 measurement comprising the steps of:

31

32 1.   Placing a standard in the reader in place of the

33      body part.

34

35 2.   Measuring the signal from the standard for each

36      wavelength and storing the values in the

1           calibration storage location.

2

3    3.    Before making a measurement of a body part,

4           placing the calibration standard in the reader.

5

6    4.    Measuring the signal from the standard for each

7           source.

8

9    5.    Comparing the just measured standard values to the

10          stored calibration values.

11

12    6.    Calculating correction factors for each source

13          wavelength.

14

15    7.    Removing the standard and placing the body part in

16          the reader.

17

18    8.    Measuring the signal from the body part for each

19          source.

20

21    9.    Adjusting the measured values using the calculated

22          correction factors.

23

24    In addition to the signal correction factors a

25    correction factor can be calculated for the instrument

26    temperature.  This can be applied to each signal with a

27    different correction coefficient.

28

29    The invention further provides a method of measuring a

30    biological parameter in a subject, the method

31    comprising the steps of:

32

33          directing one or more pulses of optical energy

34          from the exterior into the tissue of a subject

35          along a beam axis, the optical energy having a

36          wavelength selected to be absorbed by tissue

1         components of interest, thereby to produce a

2         photoacoustic interaction;

3

4         detecting acoustic energy resulting from said

5         photoacoustic reaction by means of a transducer

6         positioned to intercept acoustic energy

7         propagating in a direction other than the forward

8         direction of said beam axis; and

9

10        deriving from said detected acoustic energy a

11        measure of the parameter of interest; and a

12        corresponding apparatus.

13

14

15 Embodiments of the invention will now be described, by

16 way of example only, with reference to the accompanying

17 drawings in which:-

18

19        Figs. 1A,1B and 1C are side views illustrating the

20        principle of operation of one embodiment of the

21        present invention;

22

23        Fig. 2 is a schematic perspective view showing a

24        sensor head for use in carrying out the

25        measurement illustrated in Fig. 1;

26

27        Fig 3. is a cross section view of the sensor head

28        of Fig. 2;

29

30        Fig. 4 is a side view of the sensor head of Fig.

31        2;

32

33        Fig. 5 is a schematic perspective view of an

34        apparatus incorporating the sensor head of Figs. 2

35        to 4;

36

Fig. 6 is a perspective view illustrating an
alternative form of sensor head;

Fig. 7 is a schematic end view showing another
form of sensor head;

Figs. 8a and 8b are a cross-sectional side view
and a plan view, respectively, of a further sensor
head;

Fig. 9 is a cross-sectional side view of one more
embodiment of sensor head;

Fig. 10 is a perspective view of one type of ear
interface apparatus;

Fig. 11 is a schematic of a multiple laser optical
distribution system using lenses, mechanical
mounts and a reference detector;

Fig. 12 is a schematic of a multiple laser optical
distribution system using fiber optic cables and a
fiber Wavelength Division Multiplexer (WDM), a
beam splitter and a reference detector;

Fig. 13 is a perspective view of a finger
interface apparatus with removable inserts that
are moulded to fit one individual;

Fig. 13A shows part of the apparatus of Fig. 13 in
greater detail;

Fig. 14 is a schematic of a semi-spherical
detector that contains a hole for the light beam,
with a vacuum system and a fiber distribution
system;

1

2      Fig. 15 is a perspective view showing one form of

3      the instrument utilizing the vacuum body

4      interface, a semi-spherical detector and the

5      multiple laser source with lenses and mechanical

6      housing;

7

8      Fig. 16 is a perspective view showing one form of

9      the instrument using an ear lobe body interface,

10     with the added feature of being able to manipulate

11     the pressure on the ear lobe; and

12

13     Figs. 17, 18 and 19 are graphs illustrating an

14     example.

15

16  Referring to Fig 1, an important feature of the present

17  invention lies in introducing light energy along an

18  axis into an area of soft tissue and detecting the

19  resulting acoustic response transverse to that axis.

20  Accordingly, in the arrangement of Fig 1A light energy

21  from a diode laser (not shown) is transmitted via a

22  fibre-optic guide 10 to the tip of a finger 12.  The

23  photoacoustic interaction occurs in an approximately

24  cylindrical region indicated at 14 from which acoustic

25  energy is radiated in a generally cylindrical manner

26  and is detected by a transversely arranged acoustic

27  transducer 16.

28

29  In Figs 1B and 1C, the principle is similar.  The

30  finger 12 is pressed against a support with force F.

31  In Fig 1B, the incident light beam indicated at L is

32  directed as in Fig 1A, and the transducer 16 is at an

33  angle of 45 degrees thereto.  In Fig 1B, the angle is

34  90 degrees as in Fig 1A, but the incident beam is

35  directed differently into the fingertip.

36

1     In the present embodiment, the laser wavelength is

2     chosen to achieve high degree of absorption by glucose

3     present in the blood. A suitable wavelength is in the

4     range approximately 1000 to 3000 nm. The laser pulse

5     duration is chosen to be short, typically of the order

6     of 5 to 500 ns, in order to minimise thermal diffusion

7     and thus to optimise the acoustic waveform. For the

8     same reasons, it is desirable to use a spot size which

9     is sufficiently small to minimise thermal diffusion,

10    typically a spot size of the order of 0.05 mm to

11    0.50 mm.

12

13    The efficiency of the photoacoustic detection is also

14    influenced by the positioning and dimensions of the

15    acoustic transducer in relation to the characteristic

16    extinction length of the tissue at the principal

17    wavelengths chosen for measurement. In the fingertip

18    arrangement of Fig. 1, the system efficiency will be

19    improved by optimising the length of the transducer

20    crystal parallel to the axis of the finger, but the

21    length should not be so great as to give rise to

22    undesired signals which would occur at the point of

23    entry of the optical energy into the finger and by

24    reason of interaction of the acoustic energy with bone

25    or other hard tissue.

26

27    A second limit on the size of the acoustic detector

28    derives from the wavelength of the acoustic wave in the

29    tissue. Again making use of Huyghens principal of

30    superposition we view each point of tissue, that is

31    illuminated by the incoming light, as a point source

32    that generates a spherical pressure wave. The signal

33    measured at the detector is just the superposition of

34    all pressure waves from all points that are illuminated

35    by the source light. Normally if the size of the

36    detector is increased then the signal should also

1    increase because more energy is received by the

2    detector. However if the acoustic detector is too

3    large then a pressure wave generated from a tissue

4    element will create a pressure wave that will strike

5    the both ends of the detector. If the paths length

6    from the tissue element to the first end of the

7    detector is different than the path length to the

8    second end of the detector and if this difference in

9    path length is about one half of the acoustic signal

10   wavelength then the signal will destructively interfere

11   with itself and will reduce the magnitude of the

12   measured signal.

13

14   Referring to Fig 2, one manner of carrying out the

15   arrangement shown in Fig 1 makes use of a sensor head

16   having a finger rest 18 which is slidably moveable

17   within housing 20 closed by a front plate 22. The user

18   inserts his finger in a semi-cylindrical depression 24

19   in the finger rest 18 with the finger tip engaged

20   against an end surface 28 which includes an exit face

21   26 of the optical fibre 10. The finger is then pressed

22   downwardly against a resilient bias to enable a

23   standardised contact to be obtained between the skin

24   and the acoustic transducer. The finger tip may first

25   be dipped in water or coated with an aqueous gel to

26   improve the acoustic coupling.

27

28   Referring to Figs 3 and 4, in this preferred

29   arrangement the acoustic transducer comprises a semi-

30   cylindrical piezoelectric transducer 30. The

31   transducer 30 is provided with a backing member 32 of

32   lead or another dense substance, the rear face 34 of

33   which is shaped in irregular curves. The use of the

34   semi-cylindrical transducer 30 maximises the area for

35   reception of acoustic energy from the finger, while the

36   use of a dense backing material minimises ringing

1     effects within the transducer. Additionally, the rear

2     face 34 is shaped as shown to reduce reflection of

3     acoustic energy back towards the piezo crystal.

4

5     Fig 3 also shows the finger rest biased upwardly by the

6     use of constant tension springs 38.

7

8     Fig 5 illustrates schematically the apparatus of Figs

9     2 and 3 embodied in a self-contained, portable blood

10    monitoring apparatus including a user readout 40. An

11    apparatus of this nature allows a diabetic to monitor

12    blood glucose concentration in a convenient manner, as

13    frequently as may be desired, and in a painless and

14    discreet manner.

15

16    Other forms of photoacoustic sensor head are possible

17    within the scope of the present invention. For

18    example, Fig. 6 shows an arrangement in which a light

19    guide 50 and an acoustic transducer 52 are applied to a

20    finger 54 by means of a hinged clamp member 56. Fig. 7

21    shows a finger 60 engaged by a light guide 62 and an

22    acoustic transducer 64 which are carried on a moveable

23    assembly 66 with the finger 60 being trapped between

24    the moveable assembly 66 and a fixed anvil 68.

25

26    It is also possible to arrange the sensor head to co-

27    operate with a soft tissue surface of the body, for

28    example a soft part of the abdomen. Figs. 8a and 8b

29    show an arrangement in which a cup shaped member 70,

30    suitably of rubber, causes a light guide 72 and an

31    acoustic transducer 74 to be contacted with a bulge of

32    soft tissue 76 which may for example be drawn into

33    contact by means of a partial vacuum within the member

34    70 caused by suction through a conduit 78, or by other

35    mechanical or adhesive means.

36

1    A somewhat similar arrangement is shown in Fig. 9 in

2    which a planar mount 80 carrying a light guide 82 and

3    acoustic transducer 84 is secured to a soft area of

4    body by means of surgical adhesive 86.

5

6    Referring to Fig. 10, one method of performing

7    measurement on an ear lobe involves placing the ear

8    lobe between a fixed plate 87 and a movable plate 88.

9    The acoustic detector 89 is mounted partially

10   perpendicular that is at an acute angle, to the beam

11   axis defined as line going from the center of a lens 90

12   to the center of a window 91. It has been found that

13   the system works satisfactorily with the detector 89 at

14   an angle or 45° to the beam axis. The window 91 and

15   the detector 89 are placed in direct contact with the

16   ear and the opposite plate 88 places pressure on the

17   ear using a suitable mechanism (not shown). This

18   particular embodiment of the ear interface apparatus

19   incorporates an alignment ring 92 which is temporarily

20   attached to the ear and fits over the window housing 91

21   to aid in aligning ear into the same location every

22   time.

23

24   Referring to Fig. 11, one method of combining light

25   sources into the instrument is to use a mechanical

26   housing 93 with several holes used to align lenses 95

27   and laser diodes 94. The housing shown uses a

28   hexagonal array of seven holes. The sources and lenses

29   are arranged in such a way that they all focus to the

30   same location 96 which could be on the surface of the

31   body part. This design does not show the inclusion of

32   beamsplitters and reference detectors but they can be

33   added in an alternative arrangement.

34

35   An alternative method of combining several sources into

36   one beam is shown in Fig. 12. Several laser diodes 97

1    are shown coupled to individual fiber optic cables 131.

2    These cables 132 are combined using a fiber Wavelength

3    Division Multiplexer (WDM) 98. Alternative combination

4    methods exist including couplers and multi-fiber

5    bundles.  The combined light exits the WDM 98 in a

6    single fiber 104 and terminates at the focal point of a

7    lens 131.  This end of the fiber is imaged to the end

8    of the finger 103 to a spot 102 using another lens 130.

9    Some of the light is split off the main beam using a

10   beam splitter 100 and focused onto a reference detector

11   101 using another lens 99.  Additional reference

12   detectors and/or beamsplitters can be added to the

13   distribution system without changing its function.

14   Alternatively a reference detector could look directly

15   at the body part to measure the light reflecting off

16   the surface, as a measure of the overall light energy

17   entering the body part.

18

19   Referring to Fig. 13, another method of using a finger

20   as the body part and including removable inserts is

21   shown.  A finger 105 is inserted into an insert 106

22   that is used to customize the finger holder to a

23   particular finger.  The moulded insert 106 is placed

24   into a housing 107.  The finger 105 is placed against a

25   semi-cylindrical acoustic detector in a module 108 which

26   is also attached to the housing 107.  A cover 109 for

27   the housing 107 contains a mechanism 111 to apply

28   constant force to the finger 105.  The light beam 110

29   is introduced into the finger 105 using a suitable

30   optical distribution system (not shown).  Fig. 13A shows

31   the module 108 in greater detail.  A base 200 carries a

32   part-cylindrical piezo transducer 202 on a support 204.

33   206 indicates a coaxial connector to communicate the

34   transducer signal.

35

36   Fig. 14 shows a schematic of an alternative to the

1     vacuum arrangement shown in Figs. 8 and 9.  In this

2     system a photoacoustic reader 121 is placed against the

3     skin 113 with a semi-spherical detector 112 in contact

4     with the skin 113.  A vacuum pump 115 and vacuum seal

5     116 create a negative pressure and pull the skin 113

6     against the detector 112.  Processing electronics 119

7     energizes light sources 118 and an optical distribution

8     system 117 routes the light to the body part through a

9     hole in the top of the semi-spherical detector 112.

10    The optical distribution system 117 directs a small

11    portion of the light to a reference detector 114.  The

12    processing electronics 119 measures the signal from the

13    acoustic detector 112 and the reference detector 114

14    for each optical source 119 and calculates the glucose

15    value.  The value is displayed on a display 120.

16

17    Fig. 15 shows a similar system 125, only using another

18    type of optical distribution system 127.  Again a

19    vacuum pump 123 creates a negative pressure which draws

20    the skin up to an acoustic detector 122.  Processing

21    electronics 124 signals light sources in optical

22    distribution system 127 to illuminate and a signal is

23    generated at acoustic detector 122.  The processing

24    electronics 124 calculates the proper value and

25    displays it on a display 126.

26

27    Fig. 16 shows an alternative arrangement of a photo-

28    acoustic reader.  In this system 128, the vacuum system

29    is replaced with an ear squeeze mechanism 129 which

30    applies pressure to the ear.  An acoustic detector 130

31    detects the signals from the ear lobe.

32

33    In the most straightforward forms of the invention, a

34    single analyte such as glucose in blood can be measured

35    by using light of selected wavelengths and by measuring

36    the area or the amplitude of the received acoustic

1    pulse. It is preferable to make each measurement by

2    using a train of pulses, for example about 100 pulses,

3    and averaging the results in order to minimise the

4    effects of noise and pulse effects in the blood flow.

5

6    The accuracy of the detection system is governed, in

7    part, by the Signal to Noise Ratio (SNR) of the system.

8    Variations in the intensity and duration of the light

9    source can cause the acoustic signal to contain

10    variations. A normalization technique, such as taking

11    the ratio of the acoustic signal to the optical signal,

12    can significantly reduce the effect of the source

13    variations, thereby improving the signal to noise ratio

14    of the system. The optical signal can be measured with

15    a reference detector, or several reference detectors,

16    one for each source or one for a wavelength range. An

17    equation describing this type of normalization follows:

18

19

20    Normalized Signal    $=$

21

$$\text{Normalized Signal} = \frac{\text{Acoustic Signal}}{\text{Optical Signal}}$$

22

23    In some cases the relationship between the optical

24    signal land the acoustic signal changes with wavelength

25    and light intensity. When this is the case the

26    accuracy of the measurement can be further enhanced by

27    determining the energy dependence of the photoacoustic

28    signal. This may be determined by establishing the

29    specific relationship between the photoacoustic signal

30    land the incident energy from a set of measurements and

31    using this relationship to compensate for the non

32    linear response. An equation describing this type of

33    normalization is as follows:

34

35

36    Normalized Signal $=$

$$\text{Normalized Signal} = \frac{\text{Acoustic Signal}}{}$$

1          Scaling Factor *Optical Signal +

2          Offset

3

4  Other normalization methods can also apply. The time

5  interval between the optical pulse and the detection of

6  the acoustic signal may be used to characterise

7  physical properties such as the velocity of sound in

8  the tissue. In addition, in another embodiment of the

9  device the damping of the acoustic oscillations may be

10  used to monitor the elastic properties of the tissue

11  and, in particular, the compressibility. Both of these

12  aspects may be used in the person to person calibration

13  of the photoacoustic response.

14

15  More complex analysis of the received acoustic energy

16  is possible. For example, a time-gating technique may

17  be used to derive measurement at varying depths within

18  the tissue being examined. Alternatively, an array of

19  detectors can be employed to determine the profile of

20  the absorption of the acoustic signal at different

21  depths and locations. This depth profile will change

22  with the absorption coefficient and could be used as

23  additional information to determine the analyte

24  concentration. It is also possible to derive

25  information relating to a number of analytes of

26  interest by more sophisticated analysis of the received

27  acoustic energy wave forms, for example by analysis of

28  the frequency spectrum by Fourier transform or wavelet

29  analysis techniques.

30

31  Alternatively, or in combination with the frequency

32  techniques and multiple detectors, multiple light

33  sources can aid in the determination of the

34  concentration of a number of analytes.

35

36  There are a number of tissue features which may vary

1    from person to person or with in the same person over

2    time which impact the photoacoustic signal observed.

3    To obtain an accurate measurement of a given analyte,

4    such as glucose, it may be helpful to also determine

5    the concentration of other analytes such as haemoglobin

6    which may act as interferants. One approach is to

7    generate several distinct photoacoustic signals using

8    excitation light of several different wavelengths. For

9    example, excitation light of a wavelength of which

10    haemoglobin absorbs strongly but glucose has little if

11    any absorption could be sued to obtain a measure of the

12    haemoglobin concentration with which to normalize the

13    effect of haemoglobin on measurements made on different

14    persons or on the same person at different times.

15    These measurements which are to be normalized might be

16    based on the photoacoustic signal generated by light of

17    a wavelength at which glucose absorbs.

18

19    It is also possible to measure the concentration of

20    such interferants by other means, such as infrared

21    light absorption, and thus normalize or correct the

22    photoacoustic signal representative of the desired

23    analyte for variations in these interferants. Thus,

24    for example, the photoacoustic signal representative of

25    glucose could be corrected for variations in

26    haemoglobin concentration determined by optical

27    absorption techniques such as those taught in US Patent

28    No 5,702,284.

29

30    For the reliable and reproducible determination of

31    glucose a signal to noise ratio of at least 10,000 is

32    recommended. In this regard water is typically present

33    in human tissue of a concentration of about 50 molar

34    while glucose is present at a concentration of about 5

35    millimolar in a normal individual.

36

1  Apparatus and method embodying the present invention
2  have been found to yield accurate and repeatable
3  results. In the case of blood glucose measurement, the
4  clinical range of glucose concentration is
5  approximately 5-10 m mol/l in healthy subjects, and up
6  to 40 m mol/l in diabetics. An analysis based on
7  simple absorption models suggests that the change in
8  photoacoustic signal over this range might be as little
9  as 0.2%. The present invention has been found to
10 provide a change in photoacoustic signal of up to 140%
11 for a change in glucose concentration of 15m mol/l.
12
13 The precise mechanisms involved are not at present
14 fully understood. It is believed, however, that
15 absorption occurs primarily in body plasma and is
16 modified by the presence of glucose, and that this
17 affects beam geometry.
18
19 Example
20
21 The blood glucose levels of three individuals, one
22 normal individual, one type 1 diabetic and one type 2
23 diabetic, were followed over a two hour period
24 following each individual taking about 75 grams of
25 glucose orally in an aqueous solution by both
26 photoacoustics and direct blood measurement. The
27 results are reported in Figures 17, 18 and 19.
28 Photoacoustic measurements were made every five minutes
29 and blood measurements were made very ten minutes. The
30 blood samples were venous blood samples analysed by the
31 standard glucose oxidase method using a Yellow Springs
32 instrument. The error bands for the blood measurements
33 were derived from the literature accompanying the
34 testing instrument while those for the photoacoustic
35 results were based on the averages taken over 1000
36 pulses. The results were obtained from a configuration

similar to that illustrated in Figure 1 in which 10 was
an end of a 1 km multimode fibre optic cable which was
placed against the finger 12. The other end received
600 nanosecond pulses of 1040 nanometer light from a Q
switched Nd:YAG laser delivering 2.7 micro joules per
pulse for each measurement. Raman interactions in the
fibre caused the production of light an additional
wavelengths as set forth in the following table:

| Wavelength in nm | Average pulse energy in microJoules | Pulse width in ns | Approximate bandwidth in nm |
|---|---|---|---|
| 1064 | 2.7 | 600 | 4 |
| 1120 | 2.25 | 500 | 6 |
| 1176 | 2.0 | 450 | 8 |
| 1240 | 1.5 | 425 | 12 |
| 1308 | 0.85 | 400 | 15 |
| 1390 | 0.3 | 350 | 20 |
| 1450 | 0.1 | 350- | 20 |
| 1500 | 0.2 | 350 | 20 |
| 1550 | 0.18 | 360 | 20 |

The resulting photoacoustic signal was detected by a
5mm disc transducer with a lead backing and fed to an
amplifier and an oscilloscope. The transducer was
generally placed as 16 in Figure 1 but was not

1  precisely parallel to the beam axis; its detection
2  plane was at an angle of about 20 degrees to the beam
3  axis. The photoacoustic signal was evaluated in terms
4  of the difference in voltage signal from the positive
5  peak of the compression to the negative peak of the
6  relaxation of the acoustic pulse.
7
8  The change in photoacoustic response correlated well
9  with the change in blood glucose concentration over the
10  two hour measurement period. A correlation of 0.89 was
11  achieved on samples ranging from 4 to 35 m mol/l.
12
13  Other modifications and improvements may be made to the
14  foregoing embodiments within the scope of the present
15  invention as defined in the claims.
16

CLAIMS

1. A sensor head for use in photoacoustic in vivo
   measurement, comprising a housing shaped to engage
   a selected body part, light transmission means
   terminating in said housing so as to transmit
   light energy from a light source to enter the body
   part along a beam axis, and acoustic transducer
   means mounted in the housing to receive acoustic
   waves generated by photoacoustic interaction
   within the body part, the acoustic transducer
   means being disposed in the housing to receive
   said acoustic wave in a direction of high acoustic
   energy.

2. A sensor head according to claim 1, in which the
   acoustic transducer means is arranged at least
   partially perpendicular to the optical beam axis.

3. A sensor head according to claim 2, for use where
   the selected body part is the distal portion of a
   finger, in which the housing includes a generally
   half-cylindrical depression in which the finger
   may be placed with the light transmission means
   aimed at the end of the finger.

4. A sensor head according to any preceding claim, in
   which the acoustic transducer means comprises a
   piezoelectric transducer which is of a semi-
   cylindrical shape.

5. A sensor head according to any preceding claim, in
   which the acoustic transducer means comprises a
   piezoelectric transducer which is provided with a
   backing of lead or other dense material.

6. A sensor head according to claim 5, in which said backing has a rear surface shaped to minimise internal acoustic reflection.

7. A sensor head according to any of claims 1 to 4, in which the transducer means comprises a capacitor-type detector.

8. A sensor head according to any of claims 1 to 4, in which the transducer means comprises a piezoelectric transducer arranged generally perpendicular to the optical axis to detect the acoustic wave which is propagating in a direction opposite to the direction of propagation of the light beam.

9. A sensor head according to claim 8, in which the transducer is part-spherical with an aperture to allow access for the light beam.

10. A sensor head according to any preceding claim, including a surface wave detector for characterizing tissue properties.

11. A sensor head according to any preceding claim, including means for ensuring a consistent contact pressure between a selected body part and the acoustic transducer means.

12. A sensor head according to claim 11, for use where the selected part is the distal portion of a finger, said means being provided by mounting a portion of the housing engaged by the finger in a resiliently biased fashion against the remainder of the housing, and providing means to ensure that measurement is effected when a predetermined force

1     or pressure is applied by the subject against the

2     resilient bias.

3

4   13.  A sensor head according to claim 11, for use where

5     the selected part is the earlobe, said means being

6     provided by two plates, between which the earlobe

7     may be placed, and means for pressing the plates

8     together to apply pressure to the ear.

9

10  14.  A sensor head for use in photoacoustic in-vivo

11     measurements, comprising a housing shaped to

12     receive a removable insert; a removable insert

13     that engages a selected body part, the insert

14     being fitted to an individual, allowing for a

15     range of sizes of body parts to be used; light

16     transmission means terminating in or near said

17     removable insert so as to transmit light energy

18     from a light source to enter the body part along a

19     beam axis; and an acoustic transducer means

20     mounted in the housing or in the removable insert

21     to receive acoustic waves generated by

22     photoacoustic interaction within the body part,

23     the acoustic transducer means being disposed in

24     the housing or insert to receive said acoustic

25     waves in a direction of high acoustic energy.

26

27  15.  An in-vivo measuring system comprising in

28     combination: a sensor head as claimed in any

29     preceding claim; a light source coupled with the

30     light transmission means; and signal processing

31     means connected to receive the output of the

32     acoustic transducer means and to derive therefrom

33     a measurement of a selected physiological

34     parameter.

35

36  16.  The system of claim 15, in which the light

1    transmission means is a fiber optic distribution

2    system.

3

4    17.    The system of claim 16, in which there is a

5           plurality of light sources each connected to an

6           individual fiber and the respective fibers are

7           joined by a wavelength division multiplexer or a

8           fiber coupler.

9

10   18.    The system of claim 16 or claim 17, in which the

11          fiber optic distribution system terminates in

12          contact with the body part.

13

14   19.    The system of claim 16 or claim 17, in which the

15          fiber optic distribution system communicates with

16          the body part via optical elements such as lenses

17          and beamsplitters.

18

19   20.    The system of claim 15, in which the light

20          transmission means comprises optical elements

21          mounted in mechanical holders and arranged to

22          convey the light from the light source to a

23          location in proximity to the body part.

24

25   21.    The system of claim 19 or claim 20, in which the

26          light transmission means includes at least one

27          beamsplitter arranged in the light path to direct

28          a portion of the light to a respective reference

29          detector to measure the energy of the light

30          entering the body part.

31

32   22.    The system of any of claims 15 to 21, in which the

33          signal processing means is adapted to perform a

34          multi-dimensional processing method.

35

36   23.    The system of claim 22, in which the signal

1        processing means is adapted to perform one of

2        Classical Least Squares or Partial Least Squares.

3

4

5    24.   The system of any of claims 15 to 21, in which the

6        signal processing means comprises a Neural

7        Network.

8

9

10    25.   The system of any of claims 15 to 24, in which the

11        signal processing means is operable to analyse the

12        signals for their frequency content using one of

13        Fourier Analysis and Frequency Filtering.

14

15    26.   The system of any of claims 15 to 25, in which the

16        signal processing means additionally applies

17        techniques that use time information.

18

19    27.   The system of claim 26, in which the time

20        information processed is the time delay from

21        source trigger.

22

23    28.   The system of any of claims 15 to 25, in which the

24        signal processing means additionally applies

25        techniques that combine both frequency and time

26        information.

27

28    29   The system of claim 28, in which the signal

29        processing means performs wavelet analysis.

30

31    30.   The system of any of claims 15 to 29, in which the

32        light source is a laser light source.

33

34    31.   The system of claim 30, in which said laser light

35        source is selected from a pulsed diode laser, a

36        set of pulsed diode lasers, and a tunable laser

1       source.

2

3   32.   The system of claim 31, for use in measuring blood

4        glucose concentration, in which the light source

5        is a laser diode with a wavelength in the range of

6        approximately 600 nm to 10,000 nm and a pulse

7        duration of the order of 5 to 500 ns.

8

9   33    The system of any of claims 30 to 32, in which the

10       light transmission means is arranged to produce a

11       spot size of the order of 0.05 mm to 0.50 mm.

12

13   34.   The system of any of claims 15 to 29, in which

14       there are multiple light sources and means are

15       provided for time multiplexing the multiple

16       sources such that: each source is switched on and

17       generates an optical pulse, or a set of optical

18       pulses, the pulse, or set of pulses, generates an

19       acoustic signal that is detected by the detector,

20       and each source is pulsed in sequence until all

21       sources have been used to generate their own

22       signals.

23

24   35.   The measuring system of any of claims 15 to 34, in

25       the form of a self contained system including a

26       power supply and a readout, which may be carried

27       on the person and used at any convenient time.

28

29   36.   The system of claim 35, including facilities for

30       connection to a cellular telephone, two-way pager

31       or other communication device for routine

32       transmission of measurements taken to a central

33       data collection point.

34

35   37.   The system of any of claims 15 to 36, further

36       including means for manipulating the body part

1        under measurement and for performing additional

2        measurement of the tissue to obtain other

3        information about the state of the physiology of

4        the issue.

5

6    38.   The system of claim 37, in which said manipulating

7        means includes means for squeezing a body part,

8        such as an earlobe, and means for making photo

9        acoustic measurements at several different

10       pressures.

11

12   39.   The system of claim 37 or claim 36, including

13       temperature measurement means for measuring the

14       temperature of the body site, and in which the

15       signal processing means is arranged to apply a

16       correction to the measurements based upon the

17       temperature of the body site.

18

19   40.   The system of claim 39, further including means

20       for inducing temperatures above and below ambient

21       in the body part.

22

23   41.   The system of any of claims 15 to 40, comprising a

24       means for storing one or both of calibration

25       coefficients and operational parameters in order

26       to calibrate the instrument and to set critical

27       operational parameters.

28

29   42.   The system of claim 41, in which the signal

30       processing means is operable to adjust the

31       calibration coefficients and operational

32       parameters to be specific to a particular person.

33

34   43.   The system of claim 42, when dependent upon claim

35       14, in which the calibration coefficients and

36       operational parameters specific to a particular

1          person are contained in a storage site located in

2          the removable insert.

3

4   44.   The system of claim 43, in which additionally

5          calibration coefficients and operational

6          parameters specific to the reader system are

7          stored in the non-removable housing.

8

9   45.   The measuring system of any of claims 15 to 44,

10         further including connection means for connecting

11         the measuring system to an invasive measuring

12         system for the purpose of calibrating or adjusting

13         the operational parameters of the non-invasive

14         measuring system.

15

16   46.   The system of claim 45, in which the connection

17         means is selected from a cable link, IR link or

18         radio waves.

19

20   47.   A method of operating a measurement system as

21         claimed in claim 34 to remove instrument drift

22         from the measurement, the method comprising the

23         steps of:

24

25         1)   placing a calibration standard in the reader

26              in place of the body part;

27

28         2)   measuring the signal from the standard for

29              each wavelength and storing the values in the

30              calibration storage location;

31

32         3)   before making a measurement of a body part,

33              placing the calibration standard in the

34              reader;

35

36         4)   measuring the signal from the standard for

1        each source;

2

3    5)    comparing the just measured standard values

4        to the stored calibration values;

5

6    6)    calculating correction factors for each

7        source wavelength.

8

9    7)    removing the standard and placing the body

10        part in the reader;

11

12    8)    measuring the signal from the body part for

13        each source; and

14

15    9)    adjusting the measured values using the

16        calculated correction factors.

17

18    48.    The method of claim 47, in which a further

19        correction factor is calculated for the instrument

20        temperature.

21

22    49    A method of measuring a biological parameter in a

23        subject, the method comprising the steps of:

24

25        directing one or more pulses of optical

26        energy from the exterior into the tissue of a

27        subject along a beam axis, the optical energy

28        having a wavelength selected to be absorbed

29        by tissue components of interest, thereby to

30        produce a photoacoustic interaction;

31

32        detecting acoustic energy resulting from said

33        photoacoustic reaction by means of a

34        transducer positioned to intercept acoustic

35        energy propagating in a direction other than

36        the forward direction of said beam axis; and

1      deriving from said detected acoustic energy a

2      measure of the parameter of interest.

3

4  50   The method of claim 49, in which the parameter of

5      interest is blood glucose, and the optical energy

6      has a wavelength in the range of approximately 600

7      mm to 10,000 mm and a pulse duration of the order

8      of 5 to 500 ms.

9

10  51   The method of claim 49 or claim 50, in which a

11      train of pulses is applied and the detected

12      signals are averaged to derive said measure.

13

14  52   The method of any of claims 49 to 51, in which

15      said measure is derived from the energy of the

16      detected signal.

17

18  53   The method of any of claims 49 to 52, in which the

19      optical energy is directed into a body part which

20      is substantially composed of soft tissue and free

21      of bone.

22

23  54   Apparatus for measuring a biological parameter in

24      a subject, the apparatus comprising:

25

26      means for directing one or more pulses of optical

27      energy from the exterior into the tissue of a

28      subject along a beam axis, the optical energy

29      having a wavelength selected to be absorbed by

30      tissue components of interest, thereby to produce

31      a photoacoustic interaction;

32

33      transducer means arranged to detect acoustic

34      energy resulting from said photoacoustic reaction

35      by intercepting acoustic energy propagating in a

36      direction other than the forward direction of said

1    beam axis; and

2

3    means for deriving from said detected acoustic

4    energy a measure of the parameter of interest.

5

6    55    Apparatus according to claim 54, in which said

7          directing means incudes means for receiving a

8          selected body part such that the optical energy is

9          directed into a portion of the subject's body

10         which is substantially free of bone.

11

12   56    A method of correcting measurement of an analyte

13         based on a photoacoustic signal obtained from a

14         living being comprising determining the

15         concentration of other constituents in the being

16         which have a significant effect on the

17         photoacoustic signal and tend to vary from

18         individual to individual or over time, and

19         adjusting the measurement to remove the effect of

20         variations in the concentrations of said other

21         constituents.

22

23   57    The method of claim 56 in which the analyte is

24         glucose.

25

26   58    The method of claim 57 in which the concentration

27         of haemoglobin is determined and used to adjust

28         the measurement.

29

30   59    A method of establishing a photoacoustic signal

31         obtained from a living being comprising using the

32         ratio of the acoustic signal obtained to the

33         optical signal which generated the acoustic signal

34         to determine the concentration of an analyte

35         present in said being.

36

1    60    The method of claim 59 in which the analyte is

2            glucose.

3

4    61    A method of normalizing a photoacoustic signal

5            obtained from directing an optical beam on the

6            tissue of a living being comprising determining

7            the dependence of the photoacoustic signal on the

8            energy of the optical beam from a series of

9            measurements at different energies for the type of

10          tissue involved.

11

12

13